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The problem confronting the physician in the treatment of the average pernicious-anemia patient is twofold: (1) that of raising the red-blood-cell count to normal, and (2) of preventing neurological involvement. Both problems are solved quickly and decisively with Ampoules 'Reticulogen' (Parenteral Liver Extract with Vitamin B_1, Lilly). One-half cubic centimeter given every ten days will adequately maintain the average uncomplicated case of Addisonian pernicious anemia. Early and adequate treatment with 'Reticulogen' effectively prevents neurological symptoms. 'Reticulogen' is clinically standardized by administration to known cases of pernicious anemia. Specify 'Reticulogen' through your favorite retail pharmacy.

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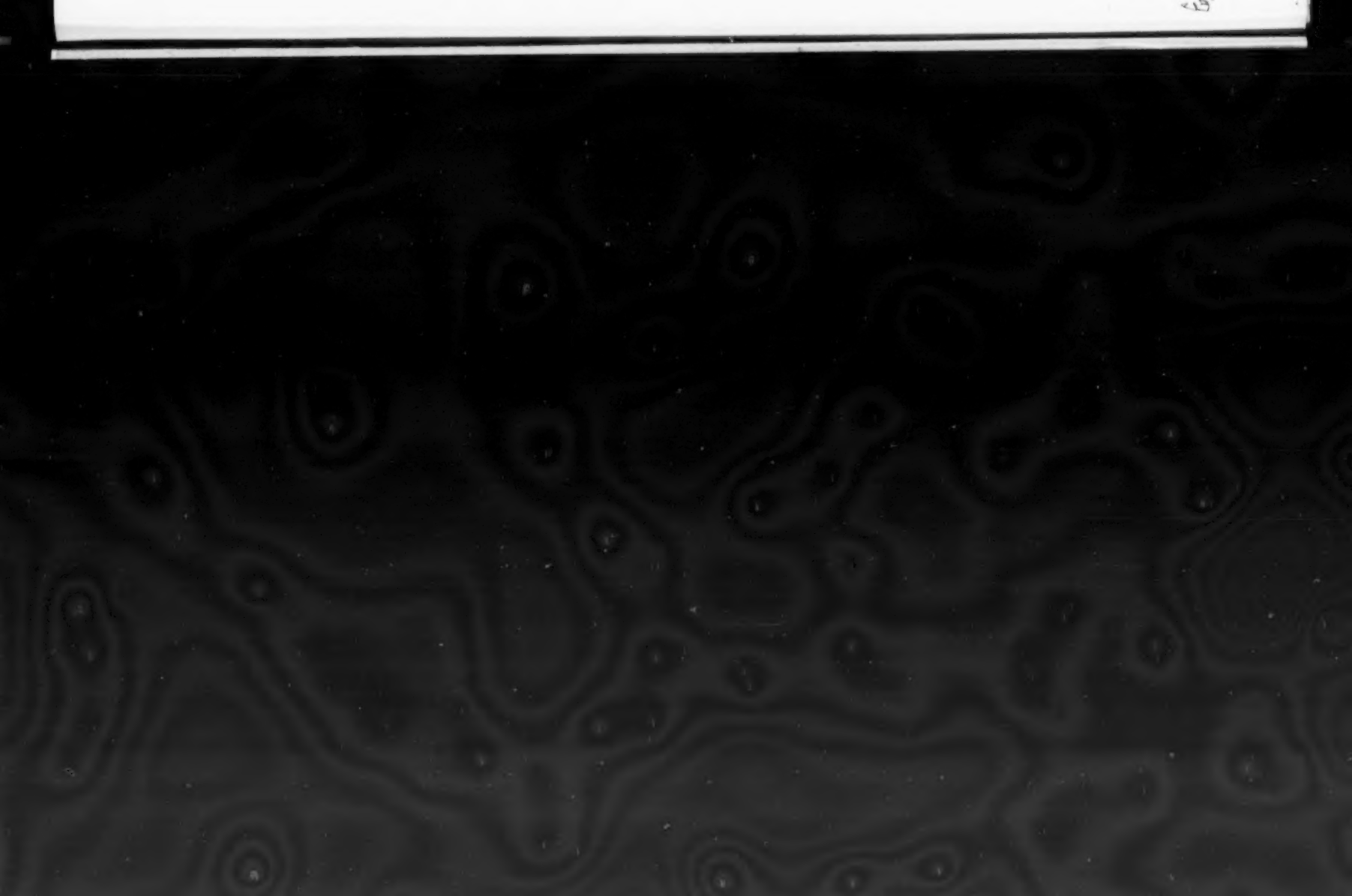

Medical
Paper

The Journal of Pediatrics

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Original Communications

STREPTOMYCIN IN THE TREATMENT OF INFLUENZAL MENINGITIS

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THE observations of Gasperini in 1890, first called attention to the fact that certain actinomycetes antagonize the growth of other microorganisms, but it remained for Waksman and his associates[1] to investigate this species systematically with regard to production of antibiotic substances. In 1942, Waksman and Woodruff[2] reported on "Streptothricin, a New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria." In 1944, Schatz, Bugie, and Waksman[3] reported a second substance, likewise obtained from one of the actinomycetes, namely streptomycin, which was derived from a strain of *Streptomyces griseus* and which proved active against gram-positive as well as gram-negative bacteria. The list of susceptible human pathogens includes at present many members of the genus Salmonella, also *Brucellosis abortus, Pasteurella tularensis, Mycobacterium tuberculosis,* as well as *Clostridium welchii, Streptococcus hemolyticus.*[4]

Although the activity of streptomycin and streptothricin in vitro is similar, the former, because of greater activity against certain pathogenic organisms and because of its lesser toxicity, appeared to present greater clinical possibilities. Reimann and associates[5] have reported its use in the treatment of typhoid fever, and others have likewise had favorable experience with the drug in the treatment of urinary tract infections,[6] tuberculous meningitis,[7] and tularemia.[8]

The present report concerns eight patients ill with *Hemophilus influenzae* type B meningitis who were treated with streptomycin either from the start of therapy or following unsuccessful treatment with other therapeutic agents.

Our first experience with the drug was in the case of a 2-year-old boy who was suffering from meningitis and bacteriemia due to *Salmonella panama.* There was no response in this particular case to sulfadiazine, and a trial of streptomycin was suggested by Dr. A. Murray Fisher. The patient was treated and recovery ensued, although it was not certain that the recovery was the the result of streptomycin therapy. No toxic manifestations were en-

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countered, however. When, some time later, a patient with influenzal meningitis failed to respond to treatment with sulfonamide and specific rabbit antiserum, the strain of *H. influenzae* isolated from the spinal fluid was tested for sensitivity to streptomycin. The sensitivity was found to be high, and it seemed likely that the infection would respond to treatment with streptomycin.

PLAN OF TREATMENT

At the time the first of these patients was treated (December, 1944) there was little prior experience with regard to the clinical use of streptomycin in systemic infections and none with regard to its intrathecal administration, hence the wide variation in the dosage in these patients. In all cases the streptomycin hydrochloride was injected both intramuscularly and intrathecally. The drug was dissolved in normal saline solution in concentrations of 4,000 to 5,000 units per cubic centimeter for intrathecal use, and in concentrations varying between 10,000 and 50,000 units per cubic centimeter for intramuscular use. The intrathecal injections were carried out twice a day, daily or on alternate days, whereas intramuscular injections were given every two or three hours.

The sensitivity of the organisms was investigated in most of the cases and several spinal fluid titers were determined. For both types of determination, a crude serial dilution method was used which consisted in adding a standard inoculum of a young broth culture of *H. influenzae* to varying dilutions of either the streptomycin solution or of the spinal fluid to be tested. Control determinations were set up, employing, in the earlier cases a strain of *Eberthella typhi*, later a strain of *Staphylococcus aureus* (Smith) obtained from the laboratories of Merck and Company, Inc.

Since we wished to obtain information with regard to the efficacy of streptomycin itself in influenzal infections, sulfonamides and specific serum were not used simultaneously with the antibiotic. Either they were discontinued (Case 1) when streptomycin was started, or their administration was begun when streptomycin therapy was thought ineffectual (Cases 4 and 8), or during convalescence (Cases 2 and 5), when sulfadiazine was given only after the patient was apparently well of his original infection. In Case 6 penicillin was used concurrently with streptomycin. In Cases 3 and 7 streptomycin was used to the exclusion of all other antibacterial therapy.

CASE REPORTS

CASE 1.—C. R. (Fig. 1). This 6-month-old white child had had a normal birth, and developmental and feeding history was normal until the present illness. The patient had been somewhat fretful five days before admission. Two days before admission the baby began to vomit frequently in a projectile fashion. The following day she had fever and a stiff neck. The day after this the temperature was still elevated, and the patient had a generalized convulsion. That night she became extremely stiff, the eyes crossed, and she seemed depressed but extremely irritable.

On admission her temperature was 100.6° F., pulse 120, respirations 30. The patient appeared to be acutely and severely ill. She was drowsy and listless but became irritable upon manipulation. Her general nutrition was excellent, though she appeared to be somewhat dehydrated. The neck was markedly stiff, both eardrums were red and bulging. Respirations were rapid and regular but shallow in character and a few scattered, moist râles were heard over both lung fields with no definite consolidation. The heart rate was rapid, but

otherwise normal. The abdomen was normal. Reflexes were generally hyperactive. Babinski's, Kernig's, and Brudzinski's signs were present. There was no paralysis of cranial or peripheral nerves. Admission spinal puncture showed 2,200 cells, 90 per cent of which were lymphocytes. Numerous gram-negative pleomorphic rods were seen which showed capsular swelling in type B *H. influenzae* serum.

Bilateral myringotomy was done, and a moderate amount of pus was obtained, which on culture yielded the influenza bacillus as well as a type XIV pneumococcus. *H. influenzae* type B was also recovered from the initial blood culture. The patient received .75 Gm. of sodium sulfadiazine intravenously, 60 mg. of immune rabbit antiserum intravenously, and 40 mg. intramuscularly. About one hour after the administration of the serum, the patient's temperature rose to 106° F., and she became extremely cyanotic. Adrenalin was given and the patient was placed in an oxygen tent and slowly improved. The patient was also given 10 mg. of heparin intrathecally. She received 100 mg. of antiserum during the first twenty-four hours, 50 the second day, 50 on the fifth day, and 25 on the sixth day, making a total of 225 mg. in six days. Spinal fluid cultures remained positive for the first seven days. Blood cultures were sterile after the second hospital day. During the first week the patient was severely ill, was in frank cardiac failure on the third day, and had convulsions on the fifth and sixth days. Her temperature remained elevated during the period of serum therapy, at a level of 102 to 104° F. Heparin was given intrathecally on three days but no significant elevation in clotting time was noted.

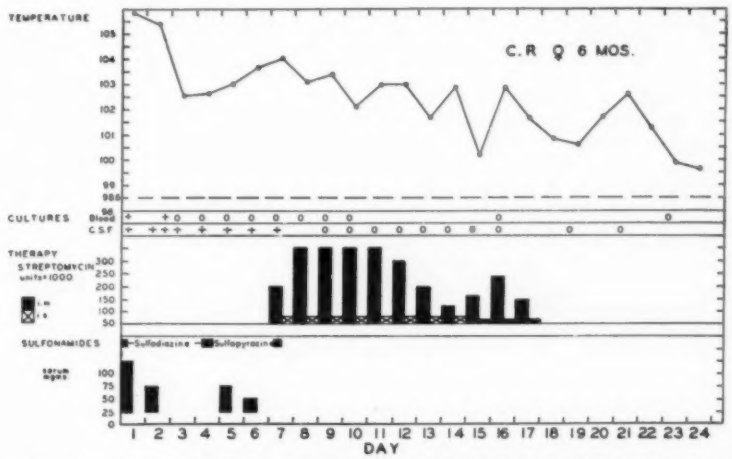

Fig. 1.—Case 1. Good response to streptomycin therapy in a 6-month-old white baby, who had been treated unsuccessfully with sulfadiazine and serum.

We had begun to despair of this patient's complete recovery because of the consistently positive spinal fluid cultures for seven days. The patient's own strain of *H. influenzae* was tested for sensitivity to streptomycin; its growth was completely inhibited by the drug in a titer of 1.2 units per cubic centimeter of culture medium. We felt, because combined serum and sulfonamide therapy had failed to control this patient's infection, that we were justified in resorting to streptomycin therapy. Therefore, on the seventh hospital day, streptomycin was given intramuscularly and intrathecally. Spinal fluid cultures were positive on the day treatment was started and negative thereafter. Streptomycin was given in a dosage of 25,000 units intrathecally for eight consecutive days followed by three intrathecal injections of 20,0000 units each. The drug was also given intramuscularly: 25,000 units every two hours for the first five days, 10,000 every two hours for the next two days, 20,000 units every two hours for the next three days, and 10,000 every two hours on the last day.

On the tenth hospital day the patient developed an urticarial rash which seemed to be a manifestation of serum sickness.

The streptomycin given intrathecally was always diluted 1:4. Nevertheless the patient seemed to develop pain at the time when the drug was injected. On streptomycin therapy the patient's temperature rose to about 103° F. every night, although she seemed to be much improved generally except for marked opisthotonus. The spinal fluid count ranged between 200 and 600 cells while streptomycin was being given. It had fallen from 2,200 to 300 cells during the period when serum was given. Streptomycin was administered for eleven days. Two spinal fluid sugars obtained during streptomycin treatment were 16 and 23 mg. per cent, respectively. In view of the patient's generally improved condition they are difficult to interpret. Spinal fluid tested for streptomycin content twenty-four hours after 25,000 units had been given intrathecally showed the presence of 60 units per cubic centimeter.

The temperature fell to normal one week after streptomycin was discontinued. By this time the meningeal signs had disappeared. One week later the cells had completely disappeared from the spinal fluid but the Pandy was still positive.

Thirteen days after streptomycin was discontinued the patient developed otitis media which responded well to sulfadiazine. Culture from the ear showed no *H. influenzae*. The baby was discharged six weeks after admission apparently recovered. She was seen in the dispensary on three subsequent occasions, at which times she seemed to be entirely well.

CASE 2.—J. G. (Fig. 2). This 15-month-old Negro patient was admitted March 6, 1945, with a history of indefinite onset approximately three to four weeks before admission, when he had fever and anorexia with a slight cold and irritability. He was treated by the local physician with one of the sulfonamides in unknown dosage. He failed to improve, ran an evening fever, continued to be irritable, lost weight, and slept poorly. On February 26, he was seen in the Harriet Lane Dispensary with a temperature of 102.6° F. He was thought to have pneumonia. Sulfadiazine therapy was ordered and he was sent home. He returned on March 6 with a temperature of 101.4° F. and a history of drowsiness and a very poor appetite for two days. Lumbar puncture revealed 4,200 cells, 90 per cent of which were mononuclears, and the smear showed organisms which were shown by means of the Neufeld quellung reaction, as well as by culture, to be *H. influenzae* type B.

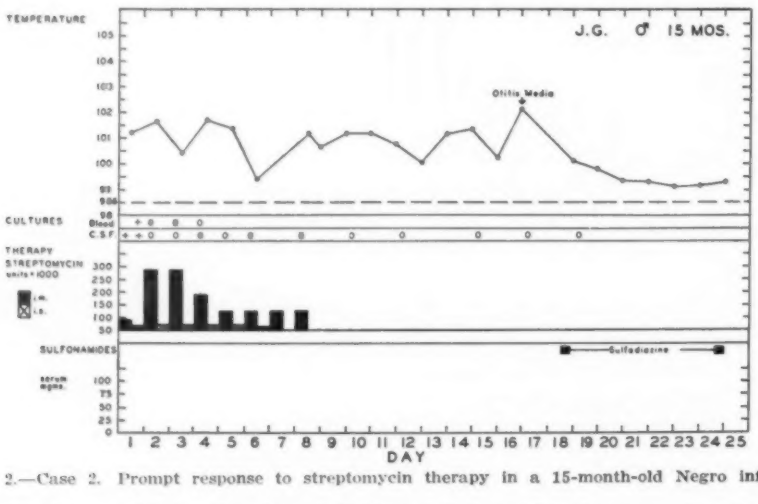

Fig. 2.—Case 2. Prompt response to streptomycin therapy in a 15-month-old Negro infant.

Physical examination showed an irritable and listless child who was moderately and acutely sick. Hydration was good. The eardrums appeared normal, the neck was extremely stiff, and the spine was rigid. Kernig's sign was negative and the remainder of the examination was not remarkable. There were no localizing neurological signs. The hemoglobin was 10.5 Gm. and the white blood cell count 19,000. One sulfadiazine level on admission

was 2.1 mg. per cent. Blood and spinal fluid cultures were positive for *H. influenzae* type B on the day of admission.

Subsequent spinal fluid cultures were sterile on eleven occasions. Nasopharyngeal cultures and cultures from both ears were negative. Blood cultures were sterile on three occasions following admission. The patient was treated with streptomycin for nine days. The first days he received 20,000 units every two hours subcutaneously and for the next five days received 10,000 units every two hours intramuscularly. Intrathecal injections were given for six days. The first five were 20,000 units and the last was 10,000 units. There was no local irritation following any of the injections. The last spinal fluid examination showed a slightly positive Pandy. The cells at all times were chiefly mononuclear cells.

The patient's clinical response lagged behind the bacteriologic improvement, but was fairly satisfactory. The convalescence was complicated by purulent otitis media, not due to *H. influenzae*. This appeared eight days after streptomycin was discontinued. The patient received no therapy other than streptomycin during the treatment of the meningitis.

This then represents a very excellent clinical response in a patient who recovered completely, whose admission blood and spinal fluid cultures were positive and all subsequent cultures were sterile.

The growth of the patient's own strain of *H. influenzae* was inhibited by 1.5 units of streptomycin per cubic centimeter of culture medium.

The spinal fluid twenty-four hours after intrathecal administration of 20,000 units of streptomycin showed a titer of 25 units per cubic centimeter. One-half hour after 20,000 units were injected subcutaneously the blood showed slightly less than 12.5 units per cubic centimeter.

CASE 3.—V. H. This patient was a 16-month-old female, admitted with a history of cough and fever for one month, with stupor and progressive spasticity of five to six days' duration. The present illness began about one month prior to admission with nasal discharge, fever, some enlargement of the cervical nodes, and progressive weakness. The patient was put to bed by order of the family physician. No specific medication was given. She ran a fever during most of the month, usually in the evening. She lost weight progressively, but her condition seemed otherwise stationary until April 7, when she began to develop stiffness of the arms and legs. Stupor developed and for two to three days prior to admission vomiting was frequent. There were no convulsions.

Physical examination showed a deeply stuporous child who appeared almost moribund. Her temperature was 100.6° F. She showed evidence of much weight loss, but of only slight dehydration. The eyes were vacant. The face was scaly, and the skin was dry and exhibited *tache cérébrale*. There were a few scattered, small, erythematous, and follicular papules. The pupils were dilated and did not react to light. The right pupil was slightly larger than the left. The fundi were essentially normal. The eardrums were clear, the neck was stiff, and respirations were irregular with short periods of apnea. There were no significant findings in the chest. The patient maintained extension of the legs, the arms were flexed and hands clenched. The tendon reflexes were generally hyperactive, but somewhat more so on the left. There was clasp knife rigidity. Tonic neck reflexes were present. Babinski's sign was present bilaterally. There was no clonus. Occasional twitchings were noticed about the corners of the mouth.

The hemoglobin was 9.3 Gm. The white blood cell count was 25,000. The spinal fluid showed 600 cells on admission, all mononuclear, and also gram-negative rods which proved to be *H. influenzae* type B. The patient's initial blood culture yielded the same organism, and the nasopharyngeal culture showed both the influenzae bacillus and a type VI pneumococcus.

The patient received intrathecal injections of 25,000 units of streptomycin each day for four days, and intramuscular injections of 25,000 units every two hours. The total dose of streptomycin was 100,000 units intrathecally and 1,025,000 units intramuscularly. The spinal fluid culture, positive on admission, was negative on the next three days. However, the patient lost ground steadily and died on the fifth hospital day. The post-mortem blood culture was sterile, but the spinal fluid obtained after death was again positive for *H. influenzae*.

This strain of influenza bacillus was inhibited in its growth by 5 units of streptomycin per cubic centimeter of culture medium.

The brain at post-mortem examination showed an extensive purulent meningeal exudate which, in places, appeared to be organized.

CASE 4.—N. W. (Fig. 3). This 8-month-old white female infant was referred to the Harriet Lane Home by Dr. Margaret Handy of Wilmington, Delaware. The present illness began, about eight or nine days before admission to the hospital, with an upper respiratory infection. Fever developed four days later, and the patient became increasingly drowsy. On the day of admission, April 15, 1945, she began to have convulsive movements of the right arm and leg. She had been taking feedings well and had not vomited. A lumbar puncture performed before admission to the hospital showed cloudy spinal fluid. Before the organism was identified, the patient received two injections of penicillin and 0.3 Gm. of sulfadiazine.

The temperature on admission was 102.5° F., pulse 160, respirations 40. The patient was a chubby infant whose excellent nutrition stood in marked contrast to her semistuporous state. There were constant clonic, convulsive movements of the right arm and the right side of the face and tongue. She responded very poorly to painful stimuli. Meningeal signs were moderately well developed and there were generally hyperactive reflexes which were most marked on the right side. The eardrums were red, thickened, and bulged slightly. There was a moderate pharyngitis. The heart was not enlarged, but the sounds were of only fair quality. There was a high-pitched blowing systolic murmur heard over the entire precordium. The remainder of the examination was not remarkable.

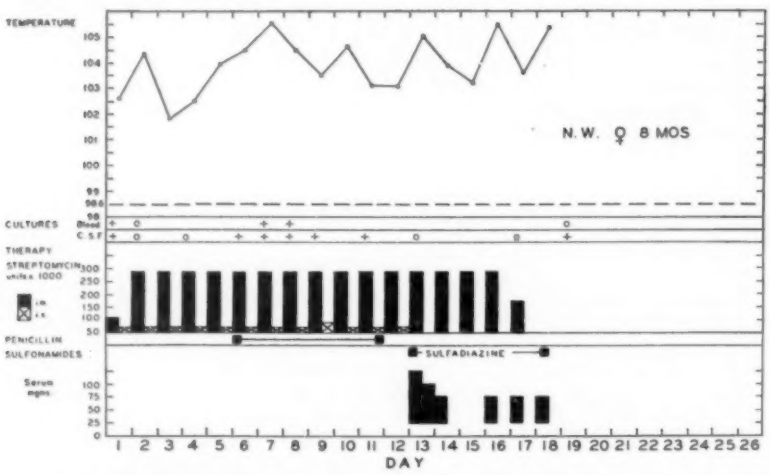

Fig. 3.—Case 4. Results of treatment of an 8-month-old white infant, who, despite large doses of streptomycin early in the course of her illness, developed a drug-fast strain of *H. influenzae* and died despite later treatment with serum and sulfadiazine.

Lumbar puncture revealed ground-glass fluid containing 980 white blood cells, 90 per cent of which were polymorphonuclear. The unspun, Gram-stained smear showed numerous gram-negative pleomorphic rods which quelled in type B *H. influenzae* antiserum. The organisms far outnumbered the white blood cells on the smear.

The patient was started on streptomycin, 20,000 units intramuscularly every two hours and 20,000 units intrathecally every day. About four hours after the beginning of treatment, she developed a temperature of 104.4° F. and showed peripheral circulatory failure with a very rapid pulse, cyanosis, and cold extremities. Intravenous fluids were given and her general condition improved during the next few hours. She was given a blood transfusion on the second day and bilateral myringotomy was performed. No influenza bacilli were isolated, although pus was obtained. On the second day the patient seemed to be slightly improved.

Blood and spinal fluid cultures on this day were sterile. In spite of her apparent general improvement, the spinal fluid became progressively more cloudy, and on the third and fourth hospital days it clotted shortly after removal. Beginning about the third day a transient flushing reaction appeared after every intramuscular injection of streptomycin. On the sixth hospital day the temperature was elevated to 104.5° F. and it was thought that a bronchopneumonia had developed on the left side. A pneumococcus type XXI was isolated from the nasopharynx at this time. The following day it was reported that the spinal fluid which had previously become sterile was again positive for the influenza bacillus. The organism, which had been inhibited in its growth by a concentration of streptomycin between 1.9 and 3.9 units per cubic centimeter of culture medium, now grew out in 250 units per cubic centimeter. On the thirteenth hospital day sulfadiazine and serum were added to the streptomycin therapy. The child's condition at this time was desperate. She went progressively downhill and died six days later, on the eighteenth hospital day.

Post-mortem culture of the blood was negative, but the spinal fluid yielded the organism on culture. Autopsy showed a severe organizing meningitis over the surface of the brain, most marked at the base. The ventricles were filled with a gelatinous, yellowish-white exudate containing small pockets of fluid.

CASE 5.—R. W. (Fig. 4). This 4-year-old white boy was referred to the Harriet Lane Home by Dr. Margaret Handy of Wilmington, Del., with a diagnosis of influenzal meningitis. The patient developed an upper respiratory infection about two weeks before admission, for which he was given sulfathiazole for two days. He developed another cold five days before admission, but this was disregarded until three days later when he awoke complaining of headache and pain in the eyes which progressed to vomiting. On the day before admission he had photophobia, a chill, and vomited four times. He became progressively more rigid on the day of admission, May 4, 1945. Lumbar puncture done by Dr. Handy revealed the presence of meningitis, and the influenza bacillus was identified by the Neufeld quellung reaction.

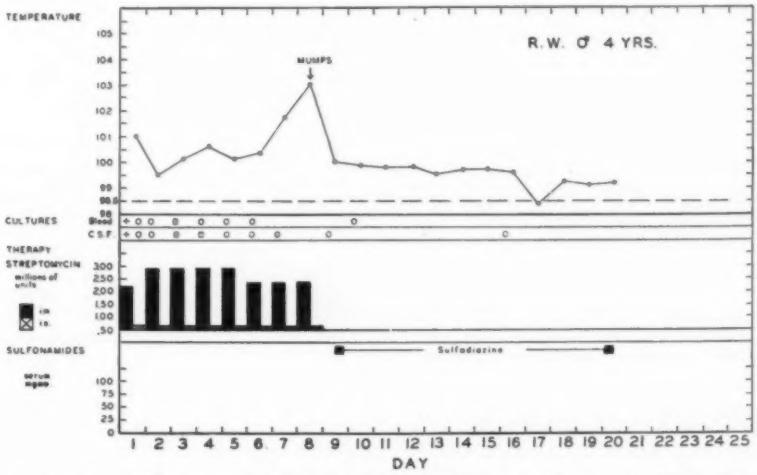

Fig. 4.—Case 5. Results of therapy in a 4-year-old white boy treated successfully with very large doses of streptomycin.

The temperature was 101° F. and the pulse rate was 120. The child was only moderately ill, rational, but somewhat irritable. General physical examination was entirely normal except for moderate inflammation of the pharynx and tonsils, a strongly positive Kernig sign, and a moderately stiff neck. Lumbar puncture showed 800 cells, almost entirely polymorphonuclear. There were a few gram-negative pleomorphic rods seen on the smear. These organisms showed capsular swelling in anti-influenza bacillus serum, type B. Streptomycin caused

complete inhibition of growth of the organism in a concentration of 12.5 units per cubic centimeter of culture medium.

He was given 40,000 units of streptomycin intrathecally and 100,000 units every two hours intramuscularly. After six doses this was raised to 200,000 units intramuscularly every two hours or 2,400,000 units per day. This dosage was continued for four days when it was decreased to 150,000 units every two hours for an additional three days. The drug was thus continued for a total of eight days.

Blood and spinal fluid cultures which were planted at 3:00 A.M. on the day of admission were both positive for type B *H. influenzae*. At 12 noon that day, both cultures were repeated, and both were found to be sterile. The spinal fluid smear at this time showed no organisms.

The patient received two or three doses of sulfadiazine before admission and the drug level taken on admission was 9.6 mg. per cent, and on the following day 5.0 mg. per cent. The temperature came down on the second day, but the patient was somewhat sicker than he had been on admission. He was difficult to arouse, but he took feedings and fluids quite well. He continued to improve with blood and spinal fluid cultures remaining consistently negative.

On the seventh hospital day the temperature rose to 101.8° F. and on the following day to 103.2° F. The patient had been exposed to a sister who developed mumps sixteen days before the patient's admission to the hospital. He showed a definite but slight swelling in the parotid gland region with no apparent inflammation of the parotid duct. The spinal fluid count on these two days showed 40 cells. The following day, the ninth hospital day, it rose to 300 cells, and on the next day to 640 cells. These elevations were believed due to mumps meningoencephalitis.[9] In both these last counts the cells were 80 per cent lymphocytes. Because we were not entirely sure that the patient had mumps and because of our experience with drug fastness in the previous case, we felt it safer to start the patient on sulfadiazine. This was done on the eleventh hospital day. The patient made an uneventful recovery. The last two lumbar punctures done on the fifteenth and nineteenth hospital days showed 10 and 6 cells, respectively. On discharge the patient was entirely well.

It was noticed about the third day that the patient developed an erythematous rash with diffuse flushing of the skin and many wheals following each injection of streptomycin. This was seen from the third day until the drug was stopped. This skin reaction disappeared in about 30 minutes. No other evidence of drug sensitivity or toxicity was noticed.

CASE 6.—C. F. (Fig. 5). This 6-month-old baby became ill five weeks before admission with an upper respiratory infection. He recovered only to relapse, and during the two weeks prior to admission the infection increased in severity. The evening before admission generalized convulsions appeared and continued intermittently through the next day.

On admission to Sydenham Hospital the patient was in a moribund, dehydrated state with a temperature of 104.4° F., pulse 160, respirations 65. The fontanel was bulging. The conjunctivae were pale and the eyes were deviated to the right with nystagmus. The posterior pharynx was filled with a purulent secretion. There was dullness at both lung bases posteriorly with many coarse, moist râles through both lung fields. The patient lay in marked opisthotonus, and the tendon reflexes were hyperactive.

The hemoglobin was 6.7 Gm.; the spinal fluid was cloudy, containing 890 white blood cells, almost all mononuclear cells. Gram-negative rods in the fluid showed capsular swelling with type B *H. influenzae* antiserum. The blood culture was sterile. The organism was inhibited by 2.0 units of streptomycin per cubic centimeter of culture medium.

On admission the patient was treated intensively with intravenous fluids and given sulfadiazine. To everyone's surprise he survived the first night in the hospital. The following morning sulfadiazine was discontinued, and therapy with streptomycin and penicillin was begun, the latter to combat the pneumonia believed due to type XI pneumococcus which was isolated from the nasopharynx.

Intramuscular streptomycin, 10,000 units every three hours, was continued for three weeks, and 10,000 units of streptomycin were given intrathecally on the first and second hospital days. Spinal fluid cultures became negative on the second hospital day, but again

were positive on the fifth day and on the seventh, at which time intrathecal streptomycin was begun again. The patient's temperature had risen to 102.4° F., and the pneumonia seemed to have spread. Intrathecal streptomycin was given in doses of 10,000 units every day for seven days and thereafter four times on alternate days.

Approximately two weeks after streptomycin was discontinued, the patient's course was complicated by a febrile episode. Nasopharyngeal cultures revealed a type XI pneumococcus, and three blood cultures yielded a *Staphylococcus albus*, perhaps a contaminant.

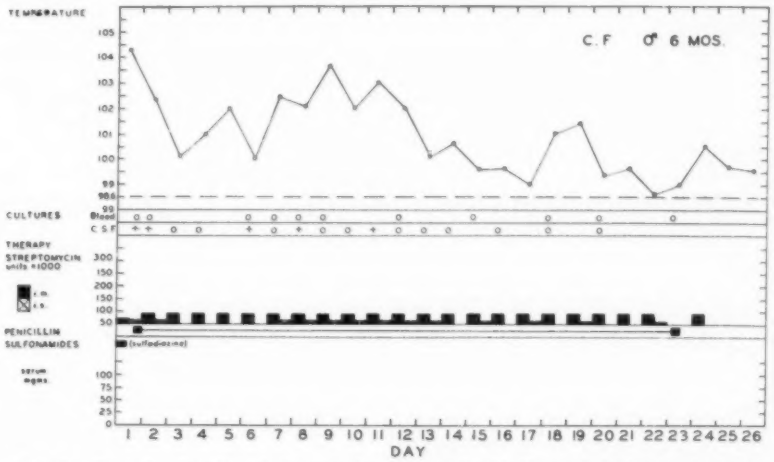

Fig. 5.—Case 6. Results of therapy in a 6-month-old Negro infant who had been ill for several weeks prior to admission. Treated with relatively small doses of streptomycin he relapsed but ultimately recovered.

Following the institution of daily intrathecal therapy, there was one positive spinal fluid culture—this on the tenth hospital day. At the end of the second month his course seemed more or less stationary with occasional elevations in temperature. Lumbar puncture on the 60th hospital day yielded clear fluid containing no cells; the culture was sterile. Signs of severe cerebral damage were present, however. The patient was both blind and deaf. A pneumoencephalogram showed enormously dilated ventricles and a remaining thin rim of cortex. The patient was discharged in this condition, as it was felt that the limits of therapy had been attained.

CASE 7.—T. A. This 11-week-old white infant weighing 5.2 kg. was admitted to the Harriet Lane Home because of meningitis. She had been a perfectly normal, healthy baby until five days before admission when she developed grunting respirations, fever, and drowsiness. Three days later she had convulsions, and the diagnosis of meningitis was established by lumbar puncture performed at the local hospital in Frederick, Maryland. The child was started on sulfadiazine and intramuscular penicillin forty-eight hours before admission. On arrival she was a limp, unresponsive, severely dehydrated baby. The pharynx was injected, the eardrums gray, but there were no meningeal signs and the lungs were clear.

The hemoglobin was 10.5 Gm., the white blood cell count 11,000, with 37 per cent young forms. The admission spinal fluid showed 1,580 cells, of which 74 per cent were polymorphonuclears. The spinal fluid sugar was 21 mg. per cent and on smear, gram-negative rods were seen which were identified by Neufeld quellung reaction and by culture as *H. influenzae* type B.

She was given 25,000 units of streptomycin intrathecally, soon after admission, and at twelve-hour intervals thereafter for a total of three doses. The drug was also given intramuscularly from the start, 100,000 units every two hours. The patient's temperature fell but her general condition remained poor, and she died after 48 hours in the hospital despite intra-

venous fluids, plasma, and blood. A spinal fluid culture on the second hospital day and another post mortem, remained sterile.

The growth of this particular strain of *H. influenzae* was inhibited by 3.9 units of streptomycin per cubic centimeter of culture medium. The spinal fluid obtained post mortem contained 130 units of streptomycin per cubic centimeter.

CASE 8.—L. M. (Fig. 6). This 6-year-old Negro male was admitted on May 6, 1945, from the Peninsula General Hospital, Salisbury, Maryland. He had been sick for about ten days with a mild cold which did not change until about four days before admission when he became drowsy. Three days before admission he complained of headache and pain in the back of the neck at which time he was started on sulfonamide therapy. Shortly afterward he was admitted to the hospital where a spinal puncture revealed cloudy fluid from which *H. influenzae* type B was cultured. Following this report the patient was transferred to Sydenham Hospital.

On admission he was found to be a spare, well-developed boy, aged 6 years, who was semistuporous. His temperature was 104° F., pulse 120, respirations 24, and blood pressure 90/60. He was very dehydrated. His pharynx was inflamed. He had a stiff neck and Kernig's sign was present. His ears and lungs were normal. The spinal fluid was cloudy with 4,500 cells, of which 60 per cent were polymorphonuclears; the Pandy was strongly positive; no sugar was present; many organisms were seen on smear and capsular swelling was readily demonstrated with type B *H. influenzae* serum. A blood culture taken on admission was sterile.

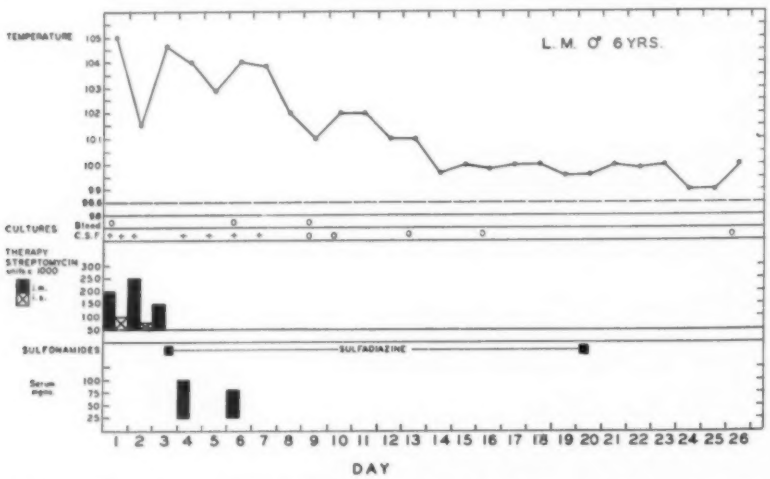

Fig. 6.—Case 8. Six-year-old Negro boy in whom three days of streptomycin therapy failed to sterilize the spinal fluid. With combined serum and sulfonamide therapy he made a good recovery.

The patient was given intravenous fluids; also 25,000 units of streptomycin intrathecally at 9:00 A.M. May 6, repeated at 8:00 P.M. that night, and again at 2:00 P.M. May 7. Intramuscular streptomycin was given on admission, 25,000 units every three hours, and continued for 2½ days.

The patient's temperature fell to 100.4° F. within eighteen hours of admission and his general condition was greatly improved. The spinal fluid examined May 7, i.e, about thirty hours after instituting streptomycin therapy, was ground-glass in appearance, with 2,430 cells, and normal sugar. No organisms were seen on smear but the culture was positive. On May 8, forty-eight hours after instituting streptomycin therapy, the spinal fluid count had fallen to 1,500, of which only 12 per cent were polymorphonuclears, the sugar was again normal, and

no organisms were seen on smear but again the culture was positive. On that day the patient's temperature had risen to 104.6° F. and it was thought inadvisble to delay further drug and serum treatment. Accordingly he was started on sulfadiazine and received 75 mg. of type B *H. influenzae* serum intramuscularly. The spinal fluid culture was positive May 9, May 10, May 11, and May 12. The patient received approximately 60 mg. of rabbit serum intramuscularly May 11. The cultures became sterile on May 14. The patient subsequently convalesced uneventfully.

DISCUSSION

The organisms isolated from the patients in this series were shown to be sensitive to amounts of streptomycin small enough to warrant hope that therapeutic levels of the drug could be attained in both blood and spinal fluid. The organisms isolated initially from different patients varied in their sensitivity, so that the concentration of streptomycin necessary to inhibit their growth ranged between 1.2 and 12.5 units per cubic centimeter of culture medium. Spinal fluid levels of streptomycin were determined in only three cases. One patient (Case 7), aged 11 weeks, showed a level of 130 units of streptomycin per cubic centimeter of spinal fluid eight hours after an intrathecal dose of 25,000 units. A second patient (Case 1) aged 6 months, had a level of 60 units per cubic centimeter of spinal fluid approximately twenty-four hours after he had received 20,000 units of the drug intrathecally. A 15-month-old baby (Case 2) showed a spinal fluid streptomycin titer of 25 units per cubic centimeter twenty-four hours after an intrathecal dose of 20,000 units. All patients were receiving the drug intramuscularly at the same time. Since four of our eight patients showed a satisfactory clinical response to the dosage selected, it is believed that adequate drug levels were maintained in both blood and spinal fluid in these cases. Our primary concern was to determine whether or not the drug was effective against the organism and to leave the most economical dosage schedules and possible adjunct therapy to later studies.

Of the four patients who recovered during treatment with streptomycin, it is believed that the drug played the predominant role in the eradication of the infection. While the first patient may have been benefited by the continued presence of circulating rabbit antibody, it seems more than coincidental that the spinal fluid became permanently sterile on the day after the start of streptomycin therapy. Furthermore, it is worth noting that the antiserum titer which had fallen persistently during the first week, necessitating several additional doses of antiserum, became stabilized following the administration of streptomycin. This probably indicates that no polysaccharide was present to combine with antibody in the serum, in other words, that the growth of organisms had been stopped. The disappearance of the bacilli from the blood and spinal fluid of the second patient was directly related to treatment with the drug, and convalescence was entirely satisfactory. In view of the experience with drug fastness in the fourth patient, the fifth patient was treated with very high doses of streptomycin, approximately two to four times higher than those received by the other patients in the series. The persistence of adequate sulfonamide levels during the first day in the hospital may also have played a role in his case. At any rate, dilutions of both blood and spinal fluid were sterile nine hours after the start of streptomycin therapy and his recovery was

dramatic. The fourth patient to have a permanent reversal of cultures had, on admission, residua of a long, untreated, and severe meningitis; in his case, penicillin was used as well as streptomycin, but since penicillin is not effective against most strains of *H. influenzae*,[10] it probably did not contribute to the sterilization of his spinal fluid.

Among these eight patients there were three deaths. The death of the third patient (V. H.) in the series was apparently due to an overwhelming infection. He was only 2 months old, an age at which the prognosis is extremely poor, and he appeared nearly moribund on admission.

The death of the fourth patient (N. W.) after transient clinical improvement was associated with a marked decrease in the sensitivity of the organism to streptomycin, i.e., the development of so-called drug fastness. Within ten days the organism, which originally was inhibited in 3.9 units of streptomycin per cubic centimeter became quite resistant to concentrations of 250 units per cubic centimeter. This experience suggests the need for using large doses of the drug initially in order to avoid the complication of drug resistance. On the other hand, should a patient under treatment not respond satisfactorily, the sensitivity of the infecting organism should again be determined.

The eighth patient in the series (L. M.) unquestionably received the streptomycin in a dosage which was inadequate for his size and age. It is of interest to note, however, that his spinal fluid count decreased, under treatment, from 4,520 to 1,500 cells per cubic millimeter, whereas, his spinal fluid sugar (as determined by the "five tube method") rose from zero to normal. The organisms, though still present on culture, were too few in number to be seen on smear; their sensitivity to streptomycin was unfortunately not determined. It should, however, be noted that the organism, which in the first culture grew only in the unstoppered culture tubes, altered its cultural characteristics following streptomycin therapy, so that it would grow only in the stoppered culture tubes, i.e., under microaerophilic conditions.

Few toxic manifestations were encountered during the treatment of these patients, and none was serious. The increase in meningeal signs during treatment of the first and fifth patients, and the failure of the spinal fluid cell count to fall steadily in patients 1, 2, and 6 after sterilization was effected, seem due to local irritation. The urine, white blood cell count, and hemoglobin showed no abnormal changes. One patient showed an erythema following injections with a dosage of 20,000 units every two hours, and another developed erythema and urticaria when receiving 150,000 to 200,000 units every two hours. The fourth patient in this series had an elevation in temperature and went into shock shortly after the first dose of streptomycin. This reaction did not recur following subsequent injections from the same lot of the drug. Reimann and associates[5] had no reaction other than pain at the site of the injection. Some of these reactions to the drug may have been due to variable impurities in the different lots, as suggested by Robinson and associates.[4d]

In this brief series of patients treated with streptomycin we wish primarily to point out that streptomycin is effective against *H. influenzae* in vivo as well as in vitro. In four patients the drug was extremely effective; in one (Case 4) it

was without effect; one patient was hopelessly ill on admission; one patient showed some response despite inadequate dosage. In view of the rapid sterilization of the blood and spinal fluid in four patients without serious toxic manifestations, streptomycin appears to have a definite, but as yet undetermined, place in the treatment of influenzal meningitis. Further experience will have to determine the proper dosage of the drug and the indications for using it simultaneously with sulfonamides and type-specific rabbit serum.

SUMMARY

1. Streptomycin is effective against *H. influenzae* type B in vivo as well as in vitro.

2. Eight patients with meningitis due to this organism were treated. Four recovered, three died, and in one, therapy was given up in favor of sulfonamide and serum.

3. Death in one case was associated with the appearance of drug fastness.

4. Toxic reactions encountered include: erythema, urticaria, augmentation of meningeal signs, persistence of pleocytosis, local pain on injection, and mild shock on initial administration. None of these was serious.

5. Streptomycin is worthy of further clinical trial in cases of infections due to *H. influenzae* type B, and also in cases of meningitis due to bacterial agents which are sensitive to this drug.

The streptomycin hydrochloride used in this study was furnished through the kindness of Dr. D. F. Robertson of Merck and Company, Inc. The potency of the several lots varied between 150 and 300 units per mg. The unit of potency was defined as "the amount of streptomycin which will just inhibit a given strain of E. coli in one ml. of nutrient broth or agar." Thus the unit of streptomycin bears no relation to the unit of penicillin. Data supplied by the manufacturers indicated that the lethal dose for 20 Gm. mice varied between 10,000 and 16,000 units according to the lot used. The pH varied between 2.6 and 7.1 in a 2 per cent aqueous solution. In mice the material was found to be pyrogen-free in doses of 5,000 to 15,000 units per kilogram.

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INFLUENZAL MENINGITIS

Report of Three Cases Treated With Streptomycin and Sulfadiazine

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INASMUCH as the use of streptomycin in the treatment of influenzal meningitis is in its infancy, we are presenting its use, concurrently with sulfadiazine, in three infants, aged 9 months, 16 months, and 15 months, in whom rapid recovery was obtained in the presence of severe influenzal infection of the meninges. The streptomycin was used both intrathecally and intramuscularly with no evidence of toxicity or undue reactions. Recoveries were complete in all three cases with no evidence of damage to the nervous system.

Case 1.—J. D., a 9-month-old white male, was admitted to the hospital Feb. 14, 1946, with a history of having been ill for three days with anorexia, vomiting, fever, and drowsiness increasing to lethargy at the time of admission. The family history was irrelevant; the past history was noncontributory.

Examination revealed an acutely ill infant, well-nourished, lethargic, with stertorous respiration, and opisthotonos. The anterior fontanel was tense; the Kernig, Babinski, and Brudzinski signs were strongly positive. The left tympanic membrane was moderately inflamed. The pharynx was slightly reddened. The eyes showed no abnormal extraocular movements. The pupils were equal and reacted to light. The temperature on admission was 101.8° F. Tissue turgor was poor. Respirations were 40 per minute, and the heart action was rapid, 140 per minute. A presumptive diagnosis of meningitis was made, and a spinal puncture was done. Cloudy spinal fluid was obtained under moderate pressure; 30,000 units of penicillin were injected intrathecally, and 50,000 units of penicillin were given intramuscularly. A clysis of 5 per cent glucose in saline was immediately started, and sodium sulfadiazine, grains 30, was given with the clysis. A maintenance dose of 50,000 units of penicillin, was continued every three hours intramuscularly, and sulfadiazine, grains 7½, with sodium bicarbonate, grains 15, was given orally every four hours. The child was placed in an oxygen tent. On the second hospital day he received 150 c.c. of whole blood intravenously. The general condition appeared improved.

A report from the laboratory gave the findings for the examination of the spinal fluid: white blood count, 3,687; polymorphonuclears, 74; lymphocytes, 26; globulin, 3 plus; glucose, 12; chlorides, 604; total protein, 123; direct smear, *Hemophilus influenzae* type B; culture, *H. influenzae* type B.

On receiving the report of the organism obtained, the penicillin was discontinued and the child continued to receive sulfadiazine. The temperature on the second hospital day reached 104.2° F. and persisted with brief daily remissions, ranging between 100 and 105° F., from February 14 to 25, when the temperature subsided to normal on February 28. The temperature was elevated from March 2 to 10, and again reached normal on March 11, from which time to discharge on April 8, it remained within normal range, except for a febrile bout of four days, March 15 to 20.

The use of streptomycin was instituted on the fourth hospital day; 50,000 μg were given intramuscularly every three hours, from February 17 to 25. Intrathecal streptomycin was given on February 17, 18, and 19: 15,000 μg dissolved in 2 c.c. of saline on the first day and 50,000 μg dissolved in 5 c.c. of saline on the other days.

From the Department of Pediatrics, Coney Island Hospital.

Sulfadiazine was continued from February 14 to March 10; on March 18, it was started again because of fever, and a spinal fluid examination showing: white blood cells, 710; lymphocytes, 95 per cent, globulin, 1 plus; glucose, 52; chlorides, 675; total protein, 120. March 19, the child developed a typical drug rash due to sulfadiazine, and it was necessary to discontinue the drug. Streptomycin was then used intrathecally, 50,000 μg on March 19, and 25,000 μg on March 21, and intramuscularly in doses of 50,000 μg every three hours on March 19, 20, 21, 22, and 23. The child improved rapidly and the temperature remained normal after this relapse, until discharge. The infant was discharged on April 8, as clinically cured; there were no evidences of nervous system involvement.

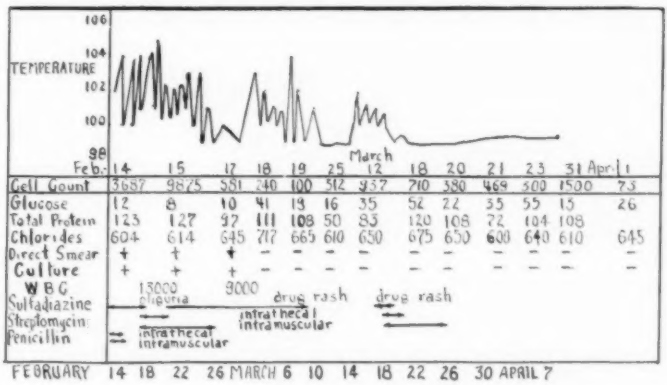

Fig. 1.

CASE 2.—A. H., a 16-month-old white female, admitted to the hospital at noon March 19, 1946, had been well (with a negative family history) until the day preceding admission, when the mother noticed that the child appeared sleepy, refused to eat, and vomited several times after taking fluids. The morning of admission the child developed convulsions, and was admitted while in a convulsive seizure.

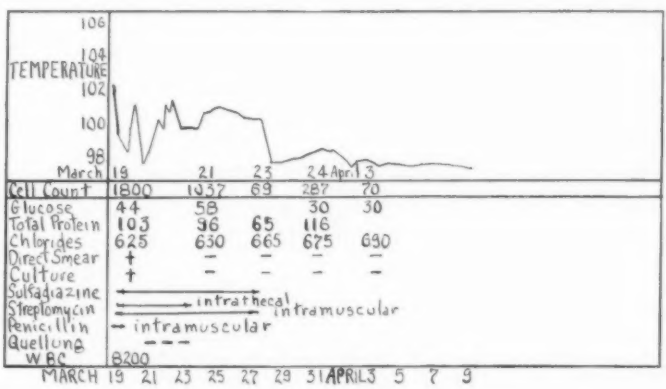

Fig. 2.

Examination revealed a well-nourished white female, cyanotic, with cold clammy skin, temperature 102.2° F., pulse 200, respirations 66. There was generalized twitching of extremities, and noisy tracheal râles. The eyelids were closed; eyeballs rolling; pupils were

equal and small. There were no abnormal reflexes. The ears, nose, and throat were normal. The lungs showed many coarse râles throughout, and some fine râles were heard at the right base.

Sodium amytal, grains 3¾, was given intravenously to control the convulsion, 3 c.c. of 25 per cent magnesium sulfate were given intravenously, and the patient was placed in an oxygen tent. During examination, a diarrheal stool was voided.

The admission diagnosis included the following possibilities:. acute toxicosis, sepsis, pneumonia, and meningitis. A spinal puncture was done while the child was in the admitting room, within four hours after admission, and a cloudy fluid was obtained under 12 mm. pressure. While awaiting a laboratory report, penicillin, 100,000 units, was given intramuscularly; adrenal cortate, aqueous extract, in doses of 3 c.c. was ordered every two hours until reaction; and an intravenous was started with Hartmann's solution; sodium sulfadiazine, grains 30, was given intravenously with a maintenance dose of grains 5 with sodium bicarbonate, grains 10 every four hours to be given orally as soon as the child was able to swallow. She was placed in an oxygen tent.

We were fortunate to receive a report from the laboratory within the hour, which identified the organism as *H. influenzae* type B. We then gave streptomycin 100,000 μg intramuscularly, and 50,000 μg every three hours to March 24; and intrathecally daily for 5 days, 50,000 μg the first three days, then 25,000 μg for two days. The streptomycin for intrathecal use was given in saline, 10,000 μg per cubic centimeter. An x-ray of the chest taken on the day of admission was negative. On the second hospital day, the temperature began subsiding, reaching normal by lysis on the ninth hospital day, after which it remained normal until date of discharge, April 9. On the second hospital day the general condition had remarkably improved, the child was conscious, began to play, and continued to improve rapidly, until well. At no time was there any evidence of toxic reaction to the sulfadiazine or streptomycin. At discharge, the child appeared perfectly well, with no evidence of neurological involvement.

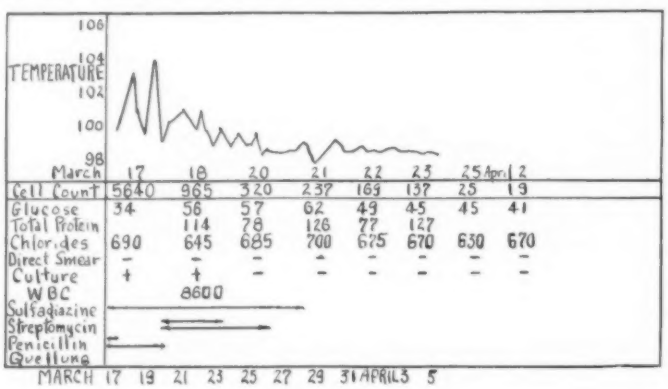
106
104
TEMPERATURE
102
100
98
March 17 18 20 21 22 23 25 April 2
Cell Count 5640 965 320 237 169 137 25 19
Glucose 34 56 57 62 49 45 45 41
Total Protein 114 78 126 77 127
Chlorides 690 645 685 700 675 670 630 670
Direct Smear – – – – – – – –
Culture + + – – – – – –
WBC 8600
Sulfadiazine
Streptomycin
Penicillin
Guaifenesin
MARCH 17 19 21 23 25 27 29 31 APRIL 3 5

Fig. 3.

CASE 3.—G. B., a 15-month-old white male, was admitted March 17, 1946, with a history of having been well until three days prior to admission, when he became irritable, vomited his breakfast, and had a fever. The following day, he vomited and had a fever of 102° F., which reached 106° F. by evening. At this time he was given Cocadiazene, which he repeatedly vomited. The third day, the temperature ranged between 100.5 and 102° F., and the child appeared restless, was moaning, and developed a swelling over the anterior fontanel. The physician treating the case advised hospitalization because of this swelling and thought a spinal puncture was indicated.

Examination revealed a well-nourished infant, apparently not very acutely ill, with temperature of 100° F., respirations 40, pulse 138, conscious, irritable, with a bulging of the

anterior fontanel (moderately tense fluctuation). The anterior fontanel measured 3 fingers by 3 fingers. There was no neck rigidity, no Brudzinski; the pharynx was slightly reddened. There was a small umbilical hernia. On admission, a diagnosis of meningitis and acute pharyngitis was made and the report of spinal fluid examination was awaited.

A cloudy spinal fluid was obtained under no pressure. With the needle in situ, 50,000 units of penicillin dissolved in 5 c.c. of saline were given. Penicillin, 50,000 units, was given intramuscularly, then 30,000 units every two hours. Sulfadiazine, grains 22½, with sodium bicarbonate, grains 45, was given orally, and maintained; and doses of sulfadiazine, grains 8, plus sodium bicarbonate, grains 15, every four hours, chloral hydrate, grains 2½, with triple bromide, grains 10, were given rectally. A subcutaneous clysis of 1,000 c.c. of Hartmann's solution was given.

On the second hospital day the diagnosis of influenzal meningitis was established by the laboratory. Streptomycin was started March 19, 50,000 μg. were given intrathecally on March 19, 20, 21, and 25,000 μg on March 22 and 23. An intramuscular dose of 100,000 μg was given, then 50,000 μg every three hours were given from March 19 to 26.

The temperature was elevated between 100° F. on admission and a high of 104° F. on the third hospital day when it slowly subsided, reaching normal on March 23, after which it remained normal to date of discharge, April 5. Clinical improvement was slow until after streptomycin was used, when the child became rapidly improved, so that on March 21, he appeared much happier, was smiling at visitors, played, took feedings well, and stopped vomiting. The fontanel by this time was normal. On March 20, the patient had a strabismus of the right eye which rapidly subsided. This was interpreted by the ophthalmologic department as due to the infectious process present at the time.

The patient was discharged on April 5 as clinically cured. There were no evidences of toxic phenomena due to the sulfadiazine or streptomycin. There was no evidence of neurological involvement.

COMMENT

The final evolution of a series of antibiotics, capable of mastering most or all of the infections, is seemingly within sight. The dream of the universal therapeutic measure may be realized by the present generation of physicians. Streptomycin has come closer to this ideal than any previous discovery. It has shown great promise in the gram-negative group of organisms, in addition to its equal influence on those organisms affected by previously known antibiotics.

In the meningitides, the meningococcus has its present drug of choice, sulfadiazine; while pneumococcus meningitis is influenced mostly by penicillin. In influenzal meningitis, the main test of treatment comes in infants under 2 years of age. Influenzal meningitis recoveries in infants under 2 years of age, before the advent of sulfonamide therapy in 1935, were reported as about 1 per cent. With the well-regulated use of the Alexander Serum and sulfonamide therapy, recovery rates as high as 80 per cent have been reported. The use of penicillin instead of serum was attended by little improvement in mortality figures. When used in treatment of children less than 2 years old, the results with the use of all these antibiotics given alone, or in combination, were poor when compared with the statistics including all age groups.

Streptomycin given in our cases resulted in more immediate results than were observed with any of the other drugs. The astonishing effects were more impressive to those who had the opportunity to observe the sudden dramatic changes occurring within a twenty-four- to forty-eight-hour period. In Case 1, penicillin and sulfadiazine were used with slow progress. The fever persisted

and there were several relapses. The penicillin apparently gave no response and was discontinued. When a severe drug rash due to sulfadiazine appeared, it became necessary to use streptomycin alone. After this was done, there was almost instantaneous response. There were no further relapses with fever, and the patient could be discharged.

The dramatic influence of streptomycin was again clearly demonstrated in Case 2. This 16-month-old infant was comatose and had convulsions on admission. On the second hospital day, the baby sat up in bed, was playful, and showed no further neurological signs. The spinal fluid culture was negative on this day, and the cell count dropped slowly. The third case, a 15-month-old infant, showed equally good response. All three cases made an uneventful recovery without complications of sequelae.

Although the dosage of streptomycin is not established, the use of 50,000 μg intrathecally daily until there is a satisfactory response clinically and on laboratory check of the spinal fluid, is indicated in view of the failure of adequate amounts of streptomycin to enter the spinal fluid after intramuscular or intravenous injections. In addition, intramuscular administration of 50,000 μg every three hours has been proved sufficient to maintain an antibacterial level in the blood stream. Treatment is continued until a total of 3 Gm. of streptomycin has been given.

The concurrent use of sulfadiazine was, in our series, because of the feeling of insecurity in the use of a new drug alone. It would be impossible for us to rule out the beneficial influence of sulfadiazine. However, should an opportunity offer itself again, and streptomycin be available, we would not hesitate to use this drug alone. Although we do not wish to draw definite conclusions from such a small series, the enthusiasm displayed by those caring for these infants was warranted by the immediate response in those cases in which the drug was started early. The specificity of the drug appeared definite.

SUMMARY AND CONCLUSIONS

1. Report is made of the treatment with streptomycin and sulfadiazine of three cases of influenzal meningitis in children less than 2 years old with recovery without complications or sequelae.

2. Fifty thousand micrograms of streptomycin were given intrathecally daily, until spinal fluid cultures were negative and clinical improvement was definite.

3. Fifty thousand micrograms of streptomycin were given intramuscularly every three hours until a total of 3 Gm. was given in each case.

4. Sulfadiazine in large doses was also given.

5. A small series does not warrant definite conclusions. However, the dramatic influence of streptomycin is significant in patients under 2 years of age where prognosis is poor even with the use of the other antibiotics.

We wish to express our appreciation for the cooperation and excellent suggestions given by Dr. John C. Hamilton, Director of Pediatrics, Coney Island Hospital.

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TRIDIONE

Its Use in Convulsive and Related Disorders

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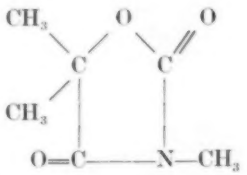
INTRODUCTION

THIS is a preliminary report of our experience with a new anticonvulsant drug, Tridione,* in the treatment of certain convulsive and related neurologic disorders.

Tridione (3,5,5,-trimethyloxazolidine-2,4-dione) has the following structural formula:



It was synthesized by Dr. M. A. Spielman for use originally as a sedative and analgesic. Although it has analgesic and slight sedative properties in nontoxic doses, it is not as effective as the opium alkaloids or the barbiturates in these respects (Richards, Everett, and Pickrell[1]). It does not affect the blood pressure or the respiratory center. During the course of its pharmacologic investigation, tridione was found to have a marked anticonvulsant effect against metrazol and electroshock in animals (Everett and Richards[2]).

In view of this reported anticonvulsant action in animals, it was decided to observe the clinical effect of tridione in certain neurologic disorders which had shown equivocal or no response to other anticonvulsant medication. A preliminary report,[3] the first to call attention to its efficacy in petit mal epilepsy and in athetosis, has been made by one of us (M. A. P.) before the Chicago Neurological Society, Jan. 9, 1945. Subsequently, Thorne[4] reported tridione to be of some benefit in the control of grand mal seizures and Lennox[5] corroborated its great value in petit mal epilepsy. We are aware that the clinical evaluation of a drug of this type is subject to many pitfalls. The clinical conditions studied are often of the type characterized by spontaneous remissions and exacerbations. Hence, unless patients are observed for relatively long periods, erroneous conclusions might easily be drawn as to the effectiveness of the medication. The conclusions from this study are based to a great extent upon our clinical impressions as well as upon the statistical evaluation of the results.

Source of Material.—This study comprises a group of 75 patients with various neurologic and convulsive disorders. They were observed for periods varying from five weeks to sixteen months. Those failing to return for regular visits are excluded from this report. The patients were seen in the Children's

From The Children's Neurology Clinic of the Cook County Hospital, Chicago, and from The St. John's Home and Hospital for Crippled Children, Springfield, Ill.

*Supplied through the courtesy of Drs. Richard K. Richards and G. M. Everett of the Department of Pharmacology, Abbott Laboratories, North Chicago, Ill.

Neurology Clinic of Cook County Hospital, Chicago, Ill., the Cerebral Palsy Center of St. John's Home and Hospital for Crippled Children, Springfield, Ill., and in private practice.

Race, Sex, and Age Distribution.—The distribution of the data by age, sex, and race is given in Table I.

TABLE I. DISTRIBUTION OF PATIENTS BY AGE, SEX, AND RACE

AGE (YR.)	SEX		RACE		TOTAL
	M	F	W	N	
Under 5	4	4	7	1	8
5 to 10	16	14	26	4	30
10 to 15	8	9	16	1	17
15 to 20	3	5	8	0	8
Over 20	8	4	9	3	12
Total	39	36	66	9	75

Of the 75 individuals observed, 39 were males and 36 were females. Only 9 of the total number were Negro. The remaining 66 were white. There was no apparent difference noted in the effectiveness or toxicity of the drug so far as sex and race were concerned.

The youngest patient was an epileptic, one year of age, while the oldest one was a 68-year-old man with tetanus. Approximately two-thirds of the patients were between the ages of 5 and 15 years and only 16 per cent (12 cases) were over 20 years of age. It was in the latter group that most of the toxic effects of the drug, such as dizziness, blurring of vision, and nausea, were encountered.

Distribution of Material by Clinical Diagnosis.—The diagnostic categories included various types of epilepsies, cerebral palsies, behavior disturbances,

TABLE II. DISTRIBUTION OF PATIENTS BY DIAGNOSIS AND SYMPTOMS

DIAGNOSIS	NUMBER OF CASES		
Epilepsy	36		
Organic brain disease		17	
Grand mal			7
Petit mal			2
Grand and petit mal			8
Idiopathic		19	
Grand mal			5
Petit mal			7
Grand and petit mal			4
Psychomotor			1
Psychomotor and grand mal			2
Tetanus	5		
Adults		3	
Children		2	
Cerebral palsy	21		
Spastics		6	
Athetoids		13	
Dystonia musculorum		2	
Chorea	2		
Parkinsonism	2		
Congenital tremors	1		
Behavior disturbance	8		
With organic brain disease		1	
With idiopathic epilepsy		5	
Functional		2	
Total	75		

chorea, Parkinsonism, congenital tremors, and tetanus (Table II). Nearly one-half (36 cases) of our series were diagnosed as epilepsy, approximately one-half (17 cases) of these being of the type due to organic brain disease, and the remainder, of the idiopathic variety.

Of the 17 patients with organic epilepsy, 7 had grand mal seizures only; 2 had petit mal symptoms only; and 8 had a combination of both grand mal and petit mal seizures. Of the group of 19 patients with idiopathic epilepsy, 5 had only grand mal seizures; 7 had only petit mal seizures; 4 had both grand and petit mal seizures; one had psychomotor attacks alone; and 2 had both grand mal and psychomotor seizures (Table II).

Five patients with tetanus* were treated, 3 adults and 2 children. There were also 2 children with severe chorea, 2 adults with Parkinsonism, and one with congenital tremors.

Of the 21 children with cerebral palsy, 6 were spastics, 13 were athetoids, and 2 had dystonia musculorum. In children with cerebral palsy, the drug was given with the aim of effecting relaxation.

Of the 8 instances of behavior disturbances, 5 occurred in children with idiopathic epilepsy, one in a child with organic brain disease, and 2 were functional.

Dosage and Criterion for Benefit.—The drug was administered generally in 5 grain doses, either in capsules or as an elixir for those unable to take the capsules or their powder contents. The dose varied from 2.5 grains twice a day to 10 grains five times a day. Generally, except for children under 6 years of age, 5 grains three times a day was found to be the optimum dose.

The appearance of drowsiness or other toxic symptoms was used as an indication for reducing the dosage. If benefit could not be obtained below the point of drowsines, the drug was deemed of no value to the patient.

Benefit was judged from the reports of the patients or their parents, nurses, or attendants, as well as from our own personal observations. Improvement was scored as:

1. *Marked*, when the benefit was dramatic and in all probability due to the drug
2. *Slight*, when the benefit was not dramatic but nevertheless noticeable
3. *No benefit*, when the status remained the same or the condition became aggravated

Whenever possible, electroencephalograms were made before and after starting tridione.†

To the tetanus patients, the drug was administered intravenously and intramuscularly. At first, intermittent dosages of single 5 c.c. ampules containing 1.0 Gm. of tridione, 0.75 Gm. of urethane, and 0.5 c.c. alcohol were used. It was found, however, that the effect of such intermittent dosage was too transient. We, therefore, resorted to the use of a continuous intravenous drip.

*These patients were on the Children's Neurology Service of Dr. A. Levinson, Cook County Hospital.

†Dr. Fredrick A. and Mrs. Erna Gibbs interpreted the electroencephalograms.

In order to eliminate the possibility that the urethane was a factor in controlling the spasm, 20 c.c. ampules containing 10 Gm. of tridione in 60 per cent alcohol were supplied. A sufficient quantity of this solution was mixed with a calculated amount of saline to maintain a constant intravenous drip over a twenty-four-hour period regulated to deliver 0.5 to 1.0 Gm. of tridione per hour. The highest dosage given was 24 Gm. of tridione in twenty-four hours, without noticeable deleterious effect.

RESULTS

In order better to evaluate our results, they are presented according to diagnostic categories.

Epilepsy Due to Organic Brain Disease.—Of the 17 patients in this group, the etiologic factors were: birth residue in 6, postinfectious encephalitis in 4, lead poisoning in 3, trauma in 3, and influenzal meningitis in one (Table III).

TABLE III. ORGANIC BRAIN DISEASE

CASE	AGE (YR.)	RACE/SEX	SYMPTOMS	ETIOLOGY	BENEFIT WITH TRIDIONE
1	5	W/M	Grand mal	Post-traumatic	Marked
2	3	W/M	Grand mal	Lead encephalopathy	None
3	7	N/F	Grand mal; hemiplegia	Lead encephalopathy	None
4	6	N/M	Grand mal; hemiplegia; shift in cerebral dominance; behavior disturbance	Measles encephalitis	None
5	7	N/M	Grand mal; focal epilepsy	Post-traumatic	Slight
6	15	W/F	Grand mal; focal epilepsy	Post-traumatic	Marked
7	7	W/F	Grand mal	Encephalitis	Slight
8	2	N/M	Petit mal	Encephalitis	Marked
9	21	W/F	Petit mal	Birth residue	Slight
10	1	W/F	Petit mal and grand mal	Birth residue	None
11	6	W/M	Petit mal and grand mal	Lead encephalopathy	Marked for petit mal
12	6	W/F	Grand and petit mal; right spastic hemiplegia	Birth residue	None
13	8	W/M	Grand and petit mal	Birth residue	None
14	12	W/F	Grand and petit mal	Influenzal meningitis	None
15	9	W/F	Grand and petit mal	Birth residue	None
16	6	W/F	Grand and petit mal	Birth residue with hydrocephalus	None
17	11	W/M	Grand and petit mal	Encephalitis	None

Therapeutically, the benefits from tridione in this group were not dramatic. In only 4 of the 17 patients was the improvement noteworthy and greater than on any other type of medication. (Table III.) Of these 4, 2 had grand mal attacks due to head trauma; one had petit mal seizures following an encephalitis, and one had both major and minor attacks as a result of a lead encephalopathy. In all of these patients, tridione was used after all the other drugs employed had failed to control the symptoms. Tridione was, in most cases, added to the previous medication, since it was generally found that tridione

CASE II TABLE 3
BEFORE TRIDIONE

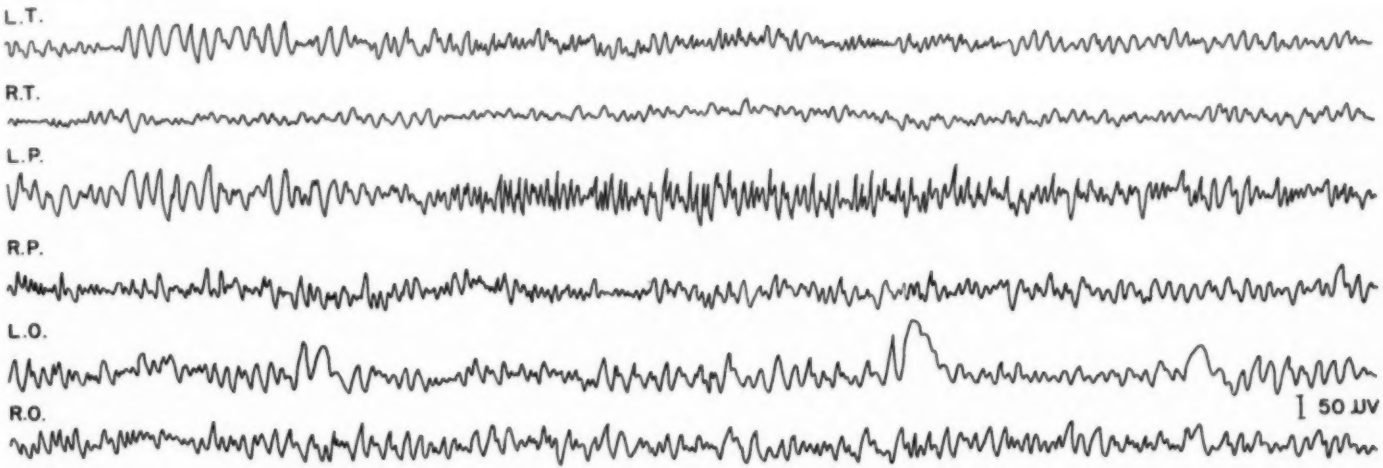


Fig. 1, A.—(Case 11, Table III). Before tridione: This patient had two to three grand mal seizures per year and twenty petit mal per week. The electroencephalogram shows a marked asymmetry between the hemispheres, with a focus of fast activity in the left parietal area and an atypical wave and spike focus in the left occipital region.

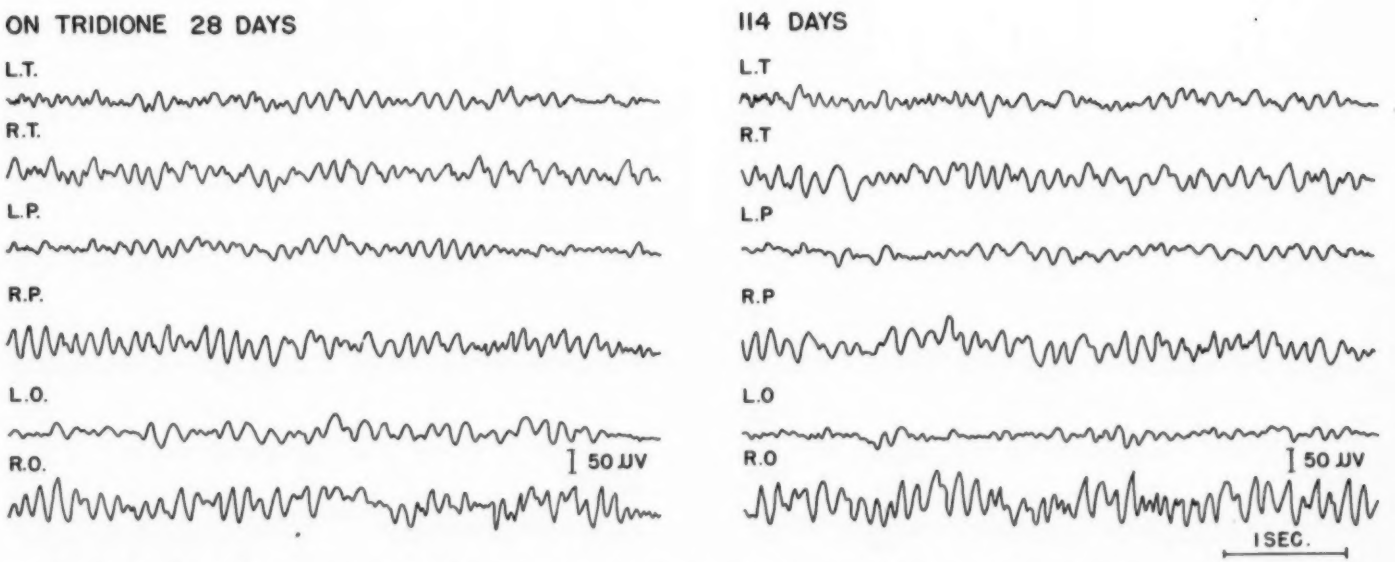


Fig. 1, B.—(Case 11, Table III.) On tridione for twenty-eight days: No grand mal and only one or two petit mal seizures occurred in this period. The electroencephalogram is greatly improved. There are no seizure discharges. The asymmetry is still present but the side of lowest amplitude is on left instead of right and all activity is moderately slow.

On tridione for 114 days: No grand mal and only one or two petit mal attacks per month in this period. The electroencephalogram shows no seizure discharges: the background activity is moderately slow and the asymmetry is still present.

alone did not control grand mal seizures as well as phenobarbital or dilantin alone. Although, in 2 instances (Cases 1 and 6, Table III) grand mal attacks were controlled after the addition of tridione to the previous medication, the greatest improvement was noted in the control of petit mal attacks in the case of which the protocol is given.

GRAND AND PETIT MAL DUE TO LEAD POISONING

(Grand mal seizures controlled with phenobarbital and petit mal seizures with tridione)

A 6-year-old white male, J. A. (Case 11, Table III), had a hemiplegia following convulsions associated with fever and coma at 18 months of age. Thereafter he developed repeated convulsions, as many as twenty daily. On phenobarbital medication the grand mal seizures became partially controlled, but petit mal seizures associated with grimacings and pulling up of the arms appeared. At the age of 6 years he was having about twenty such petit mal seizures per week and two or three grand mal attacks per year. The child was mentally deteriorated and difficult to manage.

Although there was no history of exposure to lead, laboratory studies revealed basophilic stippling in the red cells, a lead line in the epiphyses of the long bones, and 450 gamma of lead in 5 Gm. of blood. On the basis of these findings, the diagnosis of plumbism was made.

The child was given 5 grains of tridione three times a day in addition to the phenobarbital he had been taking. Almost immediately, the minor seizures decreased from 20 per week to one or two per week.

The patient remained on the same medication for fifteen months with marked improvement in his behavior and learning ability. During that period he had no convulsions and only one or two petit mal attacks per month.

The clinical improvement was reflected in the electroencephalograms (Fig. 1).

Ten of the 17 patients had no improvement on tridione. In fact, several of them seemed to get worse. In 3 instances, there was some improvement when the patients were given tridione, but the benefits were only slight or temporary, or they had to be maintained by the addition of phenobarbital and/or dilantin.

It thus appears that in epilepsy due to organic brain disease tridione may occasionally be of value in controlling either grand or petit mal attacks. This appears to be especially true in post-traumatic conditions. Of course, convulsions due to organic brain disease are generally more difficult to control by any drug than are "idiopathic" convulsions. However, it is our impression that the effectiveness of tridione as an anticonvulsant in grand mal cases generally is not as great or dependable as that of dilantin and/or phenobarbital, and that it is best used as a supplement in combination with other anticonvulsant drugs in cases not controlled by other drugs.

Idiopathic Epilepsy.—Of the 19 patients with idiopathic epilepsy (Table IV), 7 had petit mal seizures only; 5 had grand mal seizures only; 4 had both petit and grand mal seizures; one had psychomotor symptoms consisting of somnambulism; and 2 experienced both psychomotor and grand mal seizures.

In contrast to the organic epilepsies, tridione greatly benefited the majority of the idiopathic epilepsies. Thirteen of this group showed marked improvement with the drug, 3 showed slight improvement, and only 3 showed no improvement (Table IV).

TABLE IV. IDIOPATHIC EPILEPSY

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	12	W/F	Petit mal	None
2	8	W/M	Petit mal	Slight
3	6	W/F	Petit mal	Marked
4	12	W/F	Petit mal	Marked
5	11	W/M	Petit mal	Marked
6	16	W/F	Petit mal	Marked
7	11	W/F	Petit mal	Marked
8	11	W/F	Grand mal	None
9	11	W/F	Grand mal	Marked
10	3	W/M	Grand mal	Marked
11	10	W/M	Grand mal; behavior disturbance; shift in cerebral dominance	Marked
12	8	W/M	Grand mal	Slight
13	27	W/F	Grand and petit mal	Marked benefit for petit mal only
14	14	W/F	Grand and petit mal	Marked benefit for petit mal only
15	12	W/F	Grand and petit mal	None
16	9	W/F	Grand and petit mal	Marked for petit mal only
17	27	W/M	Grand mal; schizophrenia; psychomotor attacks	Marked for psychomotor and grand mal
18	16	W/F	Grand mal; behavior disturbance; psychomotor attacks	Marked for psychomotor and grand mal
19	8	W/F	Somnambulism	Marked

(A) Petit Mal: The greatest benefit from tridione was obtained in the petit mal group. Inspection of the data reveals that 6 of the 7 patients with petit mal symptoms alone had responded favorably to the drug, 5 of them dramatically, while only one had no improvement at all (Table IV). It should be mentioned that none of these children with petit mal seizures had responded to any of the previous medications such as phenobarbital, dilantin, mebaral, bromides, ammonium chloride, beta-glutamic acid, or other drugs. In fact, the common clinical observation that dilantin and phenobarbital may often precipitate petit mal seizures was, indeed, noted in 4 cases of grand mal seizures. In 3 of these 4 patients, the petit mal seizures were controlled by the addition of tridione to the previous medication. It thus appears that tridione is of value in controlling the petit mal phase of those cases with a combination of both grand and petit mal seizures.

The almost dramatic improvement of cases of petit mal appears to be more constant in the idiopathic form, rather than in that associated with organic brain disease. Table V summarizes our experience with petit mal. Since our experience with 3 patients with psychomotor attacks was similar, they are included in the table. Of the 24 patients with petit mal or psychomotor attacks, 7 of 10 who had associated organic brain disease showed either no benefit or aggravation of symptoms from tridione, while only 2 of the 14 without evidence of such organic brain disease failed to manifest improvement.

(B) Grand Mal: There were 11 patients with grand mal attacks of which

TABLE V. PETIT MAL AND PSYCHOMOTOR ATTACKS*

ETIOLOGY	NUMBER CASES	BENEFIT		
		MARKED	SLIGHT	NONE
Organic				
With grand mal	8	1†	0	7
Alone	2	1	1	0
Subtotal	10	2	1	7
Idiopathic				
With grand mal	6	5‡	0	1
Alone	8	6	1	1
Subtotal	14	11	1	2
GRAND TOTAL	24	13	2	9

*There were three instances of psychomotor attacks; two with grand mal and all of the idiopathic variety. All three responded with dramatic improvement.

†Grand mal not controlled by tridione.

‡In three of these the grand mal attacks were not controlled by tridione.

5 were markedly improved on tridione, one was slightly improved, and 5 were unimproved or aggravated. It was evident that although the drug might have some anticonvulsant effect, it was not as dependable as phenobarbital or dilantin in controlling major attacks. Its greatest value in controlling grand mal attacks was as an adjuvant or synergic drug to phenobarbital.

It was noted in several instances that whereas tridione might effectively decrease or eliminate major attacks initially the beneficial effect was not sustained, but would tend to "wear off" after a few weeks. Thus, it appears in idiopathic as well as in organic epilepsy that tridione is not a very effective primary anticonvulsant and that its greatest value in this field might be as an adjuvant or synergistic drug, especially with phenobarbital.

(C) Psychomotor Attacks: In the 3 patients with psychomotor attacks, marked benefit from tridione was seen in all. In the 2 patients also having grand mal, the drug was effective in preventing major attacks which had been incompletely controlled by phenobarbital alone.

Among the other clinical characteristics of tridione, it was our impression that greater relief from combined petit and grand mal attacks was effected when the drug was used alone, or in conjunction with phenobarbital, and less when used in conjunction with dilantin. Although this was not always the case, tridione and dilantin seemed at times to be antagonistic drugs, especially so far as control of petit mal attacks was concerned.

It was our experience that unlike phenobarbital and dilantin, tridione could be stopped suddenly without fear of precipitating a "status epilepticus." Although there was often a recurrence of attacks when the drug was withdrawn, we have not observed any exacerbation of symptoms greater than before the drug was given. To the contrary, it was often observed that once the attacks were controlled, the drug might be stopped or reduced for days or weeks without any evidences of recurrences. Several illustrative case reports follow:

PETIT MAL

(Marked benefit with tridione)

A 12-year-old white girl (Case 4, Table IV) had been having twenty to twenty-five petit mal seizures daily for four years. Neurologic examination was negative except for the fact that hyperventilation precipitated the attacks.

An electroencephalogram was typical for petit mal. The patient was given 5 grains of tridione three times a day and the attacks decreased immediately to two or three per day. The tridione was then increased to 10 grains three times a day and she became completely free from attacks for a period of 3 weeks, the first time this had occurred since the onset of the malady. Then the attacks recurred to about 4 per week. After careful questioning, it was discovered that these attacks usually occurred on Friday, during her dancing lesson. In the excitement of anticipation, she had been failing to take her medicine before dancing. After this was corrected, the frequency of attacks was reduced to two to none per week.

An electroencephalogram taken one week after tridione was started showed a definite improvement over the previous one.

The tridione was gradually decreased to 5 grains three times a day without any increase in the number of attacks, for the past twelve months, to date.

PETIT MAL

(Marked benefit with tridione)

A 16-year-old white female (Case 6, Table IV) had had petit mal attacks for eight months. These attacks were limited to the week preceding and one week during her menstrual period. At these times she would have over 100 attacks per day. The attacks could not be precipitated by hyperventilation, but generally by mental concentration as by adding columns of figures, spelling her name backwards, or sewing. She had had two grand mal attacks several years before. She had taken dilantin and phenobarbital without benefit.

The electroencephalograms showed a typical petit mal pattern (Fig. 2).

The patient was given tridione, 5 grains three times a day for about ten days before her menstrual period. This reduced her attacks before the onset of her period to twenty mild attacks on the first day. The next day tridione was increased to 10 grains three times a day and the attacks disappeared completely. She has been entirely free from seizures for the past ten months by taking the drug for the two weeks preceding and during her menstrual period. On two occasions when she ran out of medicine there were recurrences of the petit mal seizures to over 100 per day. This clinical improvement was reflected in the marked improvement in the electroencephalogram (Fig. 2).

IDIOPATHIC GRAND MAL EPILEPSY

(Controlled by phenobarbital and tridione)

An 11-year-old white girl (Case 9, Table IV) had been having convulsions since the age of 6 years. They had been increasing in frequency until she had been having an average of three to six attacks daily, most of them at night. She was given phenobarbital, 1 grain three times daily, and her convulsions were reduced to two to three per day. The addition of dilantin 1 grain three times daily resulted in no benefit. As a matter of fact, the attacks became more severe. Dilantin was therefore stopped and tridione, 10 grains three times daily, was added to the phenobarbital. Attacks immediately stopped and have not recurred for eight months in spite of reducing tridione to 5 grains three times daily.

IDIOPATHIC EPILEPSY: BEHAVIOR DISTURBANCE; SHIFT IN CEREBRAL DOMINANCE

(Marked benefit with tridione)

A 10-year-old white male (Case 11, Table IV) had convulsive seizures since 6 years of age. He had two to three such attacks per week and an associated increase in his misbehavior. He ran away from home at every opportunity, begged for money, prevaricated, and on several occasions, started fires. He had been expelled from Public School, Orthogenic School, and Parental School. His I.Q. was 120. He was ambidextrous, his dexterity tests showing a preference for the right hand, but greater skill in the left hand.

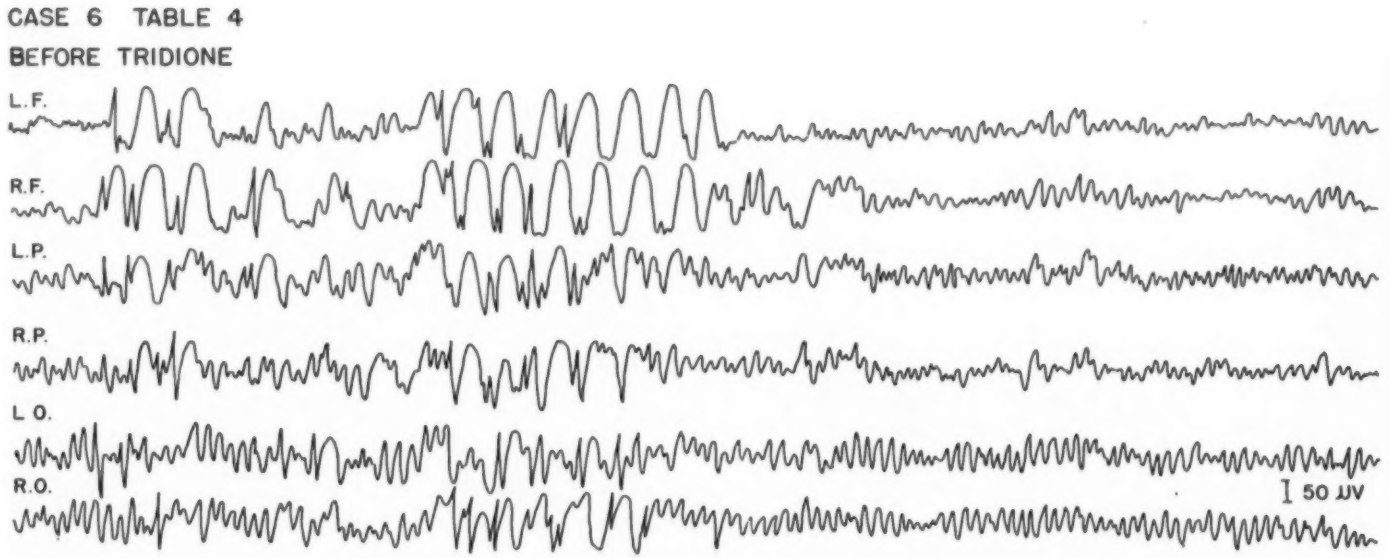


Fig. 2, A.—(Case 6, Table IV.) Before tridione: Patient has had only two grand mal attacks in her entire life, but 100 or more petit mal per day. The electroencephalogram shows frequent three-per-second wave-and-spike discharges of the petit mal type. The background activity is slightly fast.

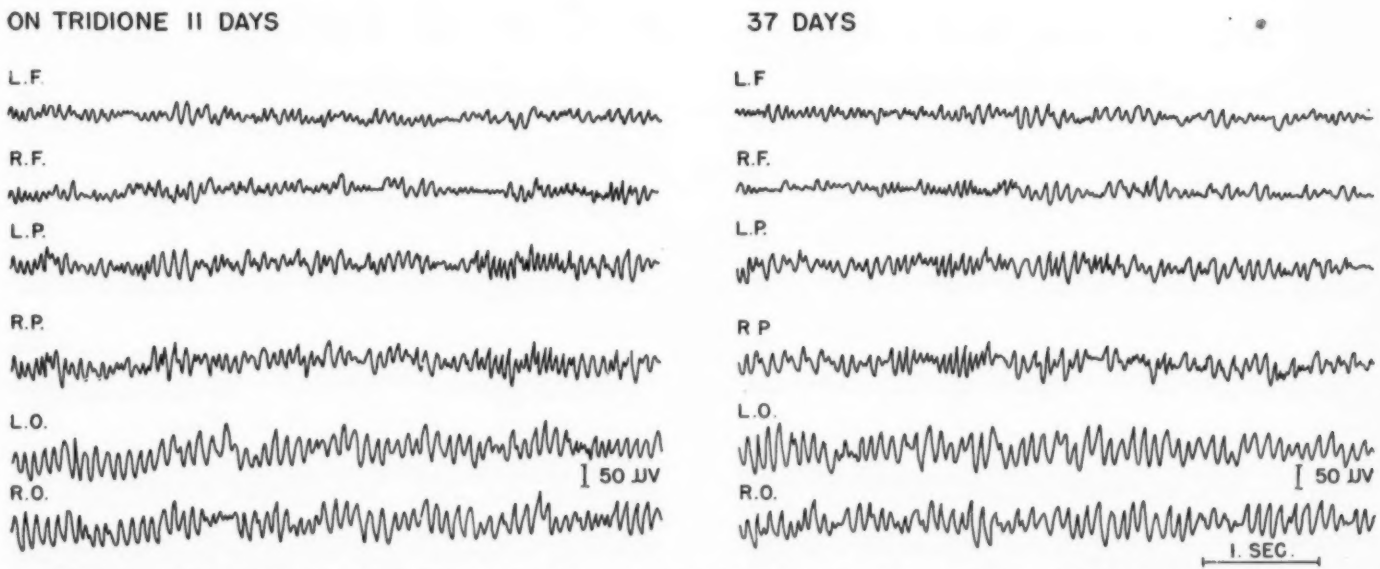


Fig. 2, B.—(Case 6, Table IV.) On tridione for eleven days and thirty-seven days: No grand mal, no petit mal. The electroencephalogram shows no spontaneous seizure discharges, and none could be elicited with hyperventilation. The background activity is still moderately fast.

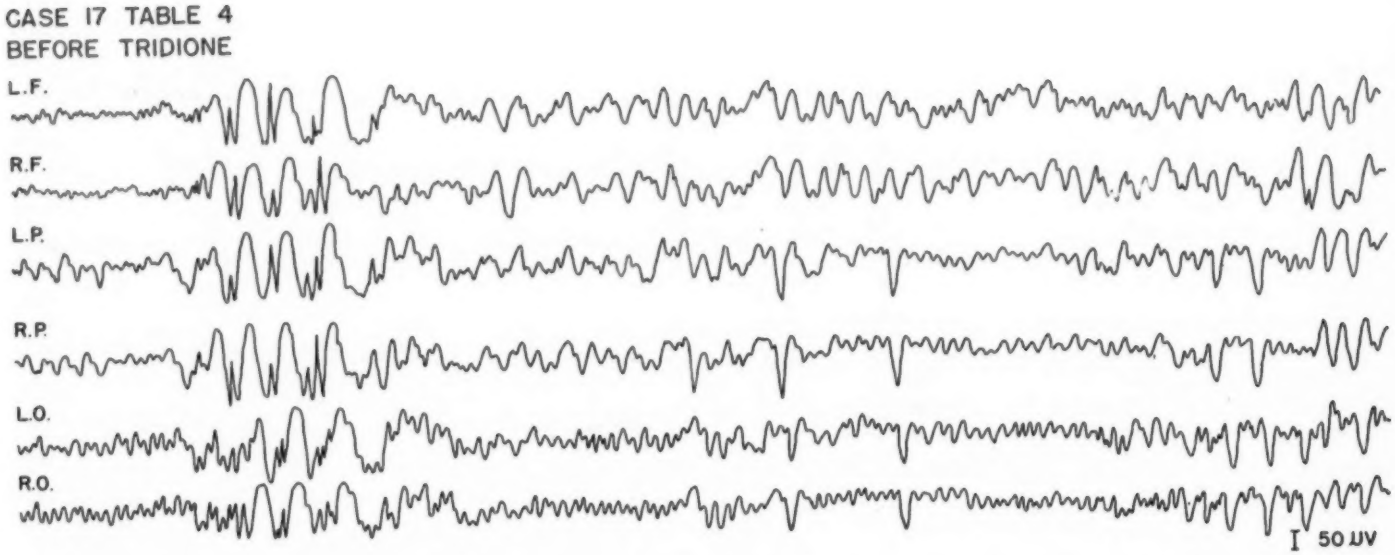


Fig. 3, A.—(Case 17, Table IV.) Before tridione: The patient had one attack of grand mal every three weeks, none of clinical petit mal, but approximately three epileptic equivalents (psychomotor seizures) per month. Electroencephalogram shows seizure discharges of the psychomotor and also of the petit mal type. The background activity is exceedingly slow.

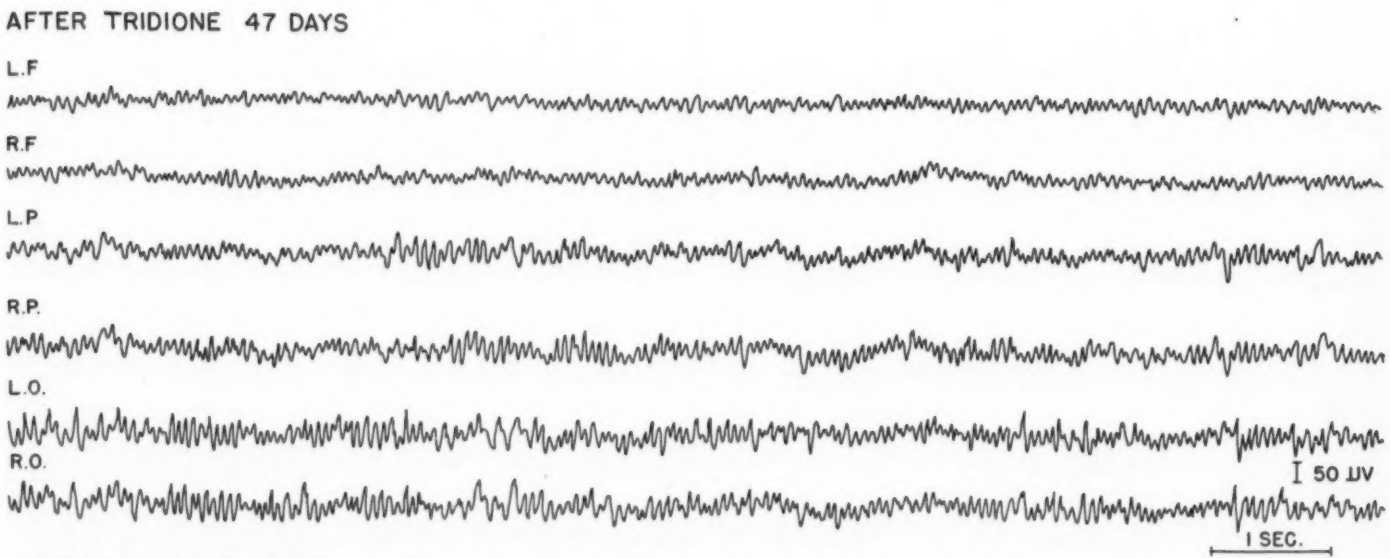


Fig. 3, B.—(Case 17, Table IV.) On tridione for forty-seven days: In this period no attacks of grand mal occurred and no epileptic equivalents (psychomotor seizures). The electroencephalogram is greatly improved. No seizure discharges are present, but moderately abnormal fast activity is present in all leads.

Phenobarbital and dilantin were not only ineffectual in controlling either his attacks or his behavior, but in fact, seemed to aggravate his condition. He was given tridione, 5 grains three times a day, and his other medication was gradually withdrawn. His behavior improved dramatically and his convulsions remained controlled for a period of several months. He still has an occasional convulsion and still presents a behavior problem but is much improved. After he had been more than one month without medication, an exacerbation occurred which was controlled by the resumption of medication.

An electroencephalogram done by Dr. E. W. Darrow before tridione was started showed an extremely high potential of hypersynchronous waves. The electroencephalogram taken when the patient was receiving dilantin and phenobarbital showed that the abnormal potentials were much increased. After tridione was started, the electroencephalogram showed a marked and dramatic improvement.

IDIOPATHIC GRAND AND PETIT MAL

(Grand mal controlled by phenobarbital; petit mal controlled by tridione)

A 27-year-old white female (Case 13, Table IV) had one or two convulsive seizures per month for the past ten years. The neurologic examination was entirely negative except for a left internal strabismus which was later corrected by surgery.

With phenobarbital and dilantin her convulsive seizures were well controlled so that she had no attacks for eighteen months. However, she developed two to ten petit mal seizures per day. These attacks could be induced by hyperventilation.

She was given tridione and the dilantin was gradually withdrawn. With the combination of phenobarbital and tridione, the petit mal seizures disappeared and the grand mal attacks remained controlled.

GRAND MAL: PSYCHOMOTOR ATTACKS: SCHIZOID PERSONALITY

(Marked benefit with tridione)

A 27-year-old white male (Case 17, Table IV) had two to five convulsions per day for the past sixteen years. With bromides and phenobarbital, the seizures decreased to one every two or three weeks. However, he was difficult to get along with at home, always sullen, and could not hold a job. There were times when he would go on drinking bouts without being aware he was doing it. He had a definite schizoid personality characterized by the feeling that people did not want to give him a chance. An electroencephalogram was abnormal with predominant very slow waves with psychomotor and petit mal discharges (Fig. 3).

The patient was then given phenobarbital, ½ grain, and tridione, 5 grains three times per day, and there was an immediate and remarkable improvement in his attitude and personality. He became happier and was able to get along with his father and mother. For the first time, he showed ambition to go into engineering work. He continued four months without attacks except for one occasion when a gas leak in the home had made the entire family ill. The improvement was reflected in the electroencephalograms taken before and after starting tridione medication (Fig. 3).

Behavior Disturbances.—In this series we observed 8 patients with severe behavior disturbances (Table VI). Five of these exhibited marked improvement with tridione, one had questionable improvement, and 2 had none at all. Two of these children, who had been expelled from school because they were too difficult to control, became much subdued on tridione and were readmitted to classes.

We do not willingly wish to convey the impression that tridione changes horns into halos and makes cherubs out of scamps. It is no substitute for psychotherapy and other accepted forms of treatment. However, as a temporary method of sedation in this type of child, it is quite often effective where barbiturates and bromides fail, suggesting that it might have a specific action in some brain center involved in behavior disturbances. In general, the bene-

TABLE VI. BEHAVIOR DISTURBANCES

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	10	W/F	Behavior problem	Marked
2	10	W/M	Behavior problem; grand mal; shift in cerebral dominance	Marked
3	6	W/M	Behavior problem; grand mal	Slight
4	14	W/M	Behavior problem; grand mal	Marked
5	10	N/M	Behavior problem; grand mal	Marked
6	9	W/M	Behavior problem; organic grand mal	None
7	16	W/F	Behavior problem	None
8	27	W/M	Psychomotor attacks; schizophrenia; grand mal	Marked

ficial effects in this type of case seem to wear off after a few weeks unless the underlying factors are corrected. Conversely, if the underlying factors are corrected, the drug can be stopped without fear of remission. An illustrative case follows:

INFANTILE REGRESSION, DESTRUCTIVE TENDENCIES AND PREVARICATION

(Benefit with tridione)

A 10-year-old white female (Case 1, Table V) developed behavior disturbances at the age of 3 years, soon after the birth of a brother. These disturbances were characterized by thumb-sucking, tantrums, enuresis, prevarication, stealing, and running away from home. She would go to the extent of cutting a screen out of a window to run away from home. Her I.Q. was 100.

She was given 5 grains of tridione three times a day and her behavior improved. She no longer strayed from home and she became more tractable. However, her enuresis persisted. She was placed in the Orthogenic School where her behavior continued to improve even without tridione.

Cerebral Palsy.—There were 21 patients seen with this diagnosis. They were divided according to the classification suggested by Phelps[6] into those with pyramidal tract lesions, the spastic group, and those with basal nuclear or other extrapyramidal lesions, which include the athetoids, rigidities, and dystonias. The spastic child exhibits evidence of an upper motor neuron lesion, such as increased deep reflexes, ankle clonus, positive Babinski, and absent superficial reflexes. In addition, he has a "stretch reflex," or reflex contraction of the involved muscle when stretched. On the other hand, in the athetoid child, the reflexes are generally all normal and there is no "stretch reflex." The outstanding features of the athetoid are the continuous involuntary motions and grimacings.

The tension in the children with the spastic type of cerebral palsy is generally involuntary and due to the stretch reflex initiated by the attempted voluntary movement. The tension in the athetoid child is voluntary in nature and due to the attempt to control the involuntary athetoid motion. The tension or spasticity in the rigidity type or those with dystonia musculorum is involuntary in nature and due to a lesion in the basal nuclei which is in some way different from that in the athetoids.

In the treatment of children with cerebral palsy, training is often impossible until the rigidity, spasticity, or tension is released. For this purpose, many methods of relaxation have been employed, e.g., heat, sedation, music,

TABLE VII. CEREBRAL PALSY

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	6	W/M	Spastic	None
2	6	W/M	Spastic	None
3	5	W/F	Spastic	Marked
4	6	W/M	Spastic	None
5	4	W/F	Spastic	None
6	5	W/M	Spastic	Slight
7	18	W/M	Athetoid	Marked
8	2	W/M	Athetoid	Marked
9	26	W/F	Athetoid	None
10	19	W/M	Athetoid	Marked
11	12	W/M	Athetoid	Marked
12	12	W/M	Athetoid	Slight
13	5	W/M	Athetoid	Marked
14	11	W/F	Dystonia musculorum	None
15	16	W/F	Athetoid	None
16	17	W/M	Dystonia musculorum	None (worse)
17	8	W/F	Athetoid	Slight
18	3	W/F	Athetoid	Slight
19	12	W/F	Athetoid	Marked
20	22	W/M	Athetoid	Marked
21	5	W/M	Athetoid	None

wilful voluntary relaxation methods. The usual sedatives are equivocal in their effects. Curare will release the tension, but its action is transient and it may be toxic when used over long periods of time.[7] Although voluntary relaxation is the ultimate goal in training, artificial relaxation may often be of value during the period of training.

In our series, 21 children with cerebral palsy were given tridione. Eight had marked benefit with the drug, 4 had slight benefit, and 9 had no benefit (Table VII). When the results are evaluated in the light of the type of cerebral palsy, it was noted that 4 of the 6 spastics and the 2 with dystonia musculorum derived no benefit from tridione. Of the 2 patients with dystonia musculorum, one was a congenital type unaffected by tridione; the second was an acquired type and became worse on the drug. This patient (Case 16, Table VII) became tense, incoordinate, complained of dizziness, and blurring of vision, and was nauseated. These symptoms were attributed to the toxicity of the drug and tridione was discontinued. Ten of the 13 children with athetosis, on the other hand, showed improvement; 7 were marked and 3 were slight. This would indicate that tridione seems to be beneficial in relieving the voluntary tension of the athetoids, but it is of little value in releasing the involuntary spasm of the spastic or of the dystonic types of cerebral palsy. A typical case report follows:

ATHETOSIS

(Improvement with tridione)

A 5-year-old white male (Case 13, Table VI) was brought to the St. John's Home and Hospital for Crippled Children, of Springfield, Ill., with such severe athetosis and tension he was unable to sit in a chair. Quinine, phenobarbital, prostigmine, and bromides failed to release the tension. After receiving tridione, 5 grains three times daily, he was able to sit comfortably, move his hands freely, and utter intelligible words. In occupational therapy and speech therapy he was able to respond well to treatment, whereas, previously, no response could be elicited.

Chorea.—Two children with chorea were treated with tridione with equivocal effect. Although there seemed to be some sedative action by the drug, we could see no remarkable benefit or any advantage over phenobarbital.

Parkinsonism.—Two patients with postencephalitic Parkinsonism, both adults, were given tridione. Both developed side-effects from the drug, with no benefit to the tremors.

Congenital Tremors.—One patient, a man 50 years old, with congenital tremors, was given tridione. He had noted that the taking of one or two cocktails (or any alcoholic beverage) had a sufficient sedative action on him to improve his writing from a rather scrawling script to a very steady one. (A similar steadying effect from alcohol is frequently observed in the athetoid form of cerebral palsy.) He noted a similar effect from taking 5 grains of tridione. When he took 10 grains of tridione he developed a slight blurring of vision.

Tetanus.—Five patients with tetanus were treated with tridione, 3 adults and 2 children. The drug was administered intravenously with the object of releasing convulsive and respiratory spasms which are often fatal in this condition.

The first patient treated was a child with a very severe tetanus who was admitted to Cook County Children's Hospital in a critical condition. This child was in a coma and had severe and frequent spasms. The intravenous tridione released the spasms, but the child died of a bronchopneumonia. This child received a total of 6 Gm. (90 grains) of tridione in twenty-four hours without apparent ill effects.

Encouraged by this response, tridione was used in the next two cases, both adults, and both with chronic alcohol addiction. A dose of 1.25 Gm. (20 grains) intravenously, controlled the patients for only one-half hour. Hence it was decided to administer the drug by continuous intravenous drip, diluting the tridione in normal saline and regulating the flow to deliver 1 Gm. of the drug every hour after an initial sedating intravenous injection was given. Even this dose of 24 grams (360 grains) in twenty-four hours was ineffectual in controlling the respiratory spasms and both patients died. Since both of these patients were alcoholics, we felt that the alcoholism may have engendered resistance to tridione as it often does to barbiturates.

The fourth patient was a child with mild tetanus. Tridione was administered by continuous intravenous drip of 10 Gm. per day for a period of three days. The convulsions were completely controlled and the child recovered without any ill effects except a mild transient hypertension which lasted about one week. Blood examination and urinalysis revealed no abnormal changes from the drug.

The fifth patient was a Negro male, 68 years of age, who was also a severe alcoholic addict. In spite of the continuous intravenous administration of tridione, the patient died in a respiratory spasm.

In the tetanus cases no definite conclusions can be drawn as to the value of the drug. It seems to be effective in controlling the tetanic spasms in children but not in alcoholic adults. It shows some promise in this condition and should be further investigated.

TOXICITY

Side-effects have been mentioned from the oral administration of the drug. It has produced nausea, vomiting, dizziness, and visual disturbances such as photophobia, blurring, and changes in color, form, and perception. In large doses, it had a sedative or soporific effect. In our series there were relatively few side-effects noted; in fact, some of the patients received as much as 50 grains of tridione per day orally without toxic symptoms. One 12-year-old child with petit mal not controlled by the drug, developed transient visual impairment and at times was unable to see his mother. Counting even the mild complaints, the incidence of toxic symptoms in our series was less than 10 per cent for the whole group. Of the adults, approximately 40 per cent showed some side-effect, such as visual disturbance or dizziness. In cases of tetanus in which patients received as much as 24 Gm. of tridione in twenty-four hours for a period of two days, no toxic symptoms were noticed.

From our experience, the drug does not seem to have any effect on the respiratory center, blood pressure, or the digestive system. No drug rashes were seen.

Some of our patients received tridione for a period of sixteen months. Although the drug was taken regularly three to four times a day, no evidence of a tendency to addiction or tolerance was noticed. All toxic symptoms observed rapidly disappeared upon discontinuing the use of the drug.

Thus, it appears that the drug has a wide range between its therapeutic and toxic dosages. It seems to be much better tolerated by children than by adults. Chronic alcoholism apparently increases the resistance to the anticonvulsant action of the drug.

COMMENT

In reviewing our experience with tridione, it appears that the drug is of least benefit in those patients with pyramidal system lesions; it is more effective when epilepsy is idiopathic than when it is associated with organic involvement of the pyramidal system. It appears to be more effective in the athetoid form of cerebral palsy than in the spastic form. Its ineffectiveness in 3 chronic alcoholics, coupled with the observation that it had a salutory effect similar to that derived from alcohol in a patient with congenital tremors, might suggest a similar nuclear site of action for both drugs. From Table VIII, it is evident that whereas the drug was of marked benefit in only 4 of 21 patients with pyramidal system involvement, it was of marked benefit to 27 of 49 patients with extrapyramidal system pathology.

One might speculate from these results, and from the suggestion of Everett and Richards[2] that the marked anticonvulsant effect of tridione against metrazol may be indicative of a subcortical action, that the site of action of tridione is not primarily on the cortex or pyramidal system but most likely on some of the lower centers in the basal nuclei or midbrain, or possibly upon the cortical connecting system of these lower centers. This might also explain the beneficial effects in the behavior disturbances. Since the greatest benefit from tridione is in the petit mal group, it might lend some credence to the view that petit

TABLE VIII. COMPARATIVE RESULTS WITH TRIDIONE BY SITE OF PATHOLOGY*

	DIAGNOSIS	NUMBER CASES	BENEFIT WITH TRIDIONE		
			MARKED	SLIGHT	NONE
	Pyramidal system lesions				
	Organic brain disease with convulsions	15	3	2	10
	Spastic cerebral palsy	6	1	1	4
	Total	21	4	3	14
	Extrapyramidal system lesions				
Effective	Idiopathic epilepsy, grand and petit mal	19	14	2	3
Effective	Petit mal (organic)	2	1	1	0
Effective	Athetoid cerebral palsy	13	7	3	3
Effective	Behavior disturbance	8	5	1	2
Effective	Congenital tremors	1	0	1	0
	Subtotal	43	27	8	8
Not effective	Dystonia musculorum	2	0	0	2
Not effective	Chorea	2	0	0	2
Not effective	Parkinsonism	2	0	0	2
	Subtotal	6	0	0	6
	Grand total	49	27	8	14

*The 5 cases of tetanus are omitted from this table.

mal might not arise primarily from a disturbance in the cortex, but rather from the midbrain as suggested by Penfield and Erickson,[8] and that the abnormal waves observed in the cortex in the electroencephalograms are secondary to this primary subcortical disturbance. One might further speculate that tridione is selective in its action, even so far as the basal nuclei and/or midbrain is concerned, for it is apparent that not all diseases characterized by basal nuclear lesions are benefited. Thus, of 6 patients with symptomatology attributable to organic or physiologic pathology in the basal nuclear regions (2 each with dystonia musculorum, Parkinsonism, and chorea), none was benefited. In fact, 3 of these patients (1 with dystonia, and 2 with Parkinsonism) experienced aggravation of their symptoms with tridione. Further pharmacologic and clinical studies will be necessary to confirm or disprove the suggestion that tridione might act on certain specific centers in the basal nuclei and/or midbrain.

SUMMARY

Clinical experience with a new drug, tridione, over a period of 16 months in 75 patients with convulsive and related disorders has left us with the following impressions:

1. It is the most effective drug yet employed in the treatment of petit mal.

2. Its anticonvulsant effect in the control of grand mal attacks is not as great as that of dilantin sodium, phenobarbital, or the bromides. It may occasionally be of value as an adjuvant or additional remedy in the control of major attacks not adequately controlled by other drugs.

3. It is more effective in idiopathic than in organic epilepsy.

4. It is of value in reducing the tension or rigidity of patients with cerebral palsy. Of these, the athetoids are benefited more than the spastics.

5. It may be of value in the temporary control of children with behavior disturbances.

6. It is of possible value in the control of the convulsions and respiratory spasms of tetanus when given intravenously.

7. It is of no particular value in chorea, Parkinsonism, or dystonia musculorum.

Regarding its clinical pharmacologic properties, it has been our experience that:

a. Tridione is a safe drug to use since no permanent deleterious effects, addiction, or tolerance were noted.

b. Toxic symptoms are usually mild and consist of photophobia, visual blurring, dizziness, and nausea. They occur more commonly in adults than in children and disappear promptly when the drug is withdrawn.

c. Sudden stopping of the drug in epilepsy does not result in status epilepticus.

d. When used in combination, it is more effective with phenobarbital than dilantin.

e. Chronic alcoholism increases the tolerance to the drug.

f. Since it is least effective in lesions of the pyramidal system and more effective in certain conditions with extrapyramidal lesions, it is suggested that its site of action is probably in the midbrain, and/or areas in the basal nuclei, and/or upon the cortical connecting tracts of these areas.

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A COMPARISON OF THE VITAMIN C IN MOTHERS AND THEIR NEWBORN INFANTS

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THE plasma ascorbic acid concentration of the newborn infant and of cord blood has been shown to be considerably higher than that of the maternal blood.[1] This has suggested the important concept that the fetus takes its supply of vitamin C whether or not the mother has a sufficient amount. However, as has been pointed out in *Nutrition Reviews*[2] the "plasma ascorbic acid levels are notoriously labile and dependent on recent dietary intake. Determination of tissue vitamin C, or of the values in white blood cell—platelet fraction of blood, would provide more convincing evidence of true maternal-fetal relationships."

We have worked with an intradermal test[3] for vitamin C. This test is based on the intradermal injection of a dye which will be decolorized by vitamin C. Slow decolorization of the dye would indicate that the tissues have an insufficient amount of vitamin C. Rapid decolorization would indicate a sufficient amount.* In our test enough of a N/300 solution of sodium 2,6-dichlorphenol indophenol is injected to raise an approximately 4 mm. wheal. A skin test time (time for disappearance of dye) of 14 minutes or more suggests a definite degree of tissue unsaturation, from 10 to 13 minutes is borderline, and less than 9 minutes, a normal amount of vitamin C in the body tissues.[3]

PLAN OF STUDY

A comparison of the vitamin C in the tissues of mothers and their newborn infants was to be made by means of the intradermal test. The intradermal test for vitamin C was done on mothers and their infants as soon after birth as possible. Tests on the infants were repeated every other day until discharge from the hospital. All intradermal tests were done in duplicate. There was no attempt at selection of patients.

RESULTS

Seventy-seven mothers and their newborn infants were tested. The first test on the infants was done within the first twelve hours after birth. The results are found in Table I. The intradermal test times for disappearance of the dye were practically always shorter in the newborn infant than in the mother. Although thirty-two of the mothers had intradermal test times of 10 minutes or longer, only one infant (Case 73) had longer than 10 minutes. In following that particular infant on subsequent days the intradermal test became similar to the others.

In fact, the intradermal test times in almost all of the newborn infants were within the range that we have come to believe indicates approaching saturation,

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*Plates of the test appear in J. PEDIAT. 28: 134, 1946.

TABLE I. INTRADERMAL TEST TIMES OF MOTHERS AND THEIR NEWBORN INFANTS

CASE	RACE	MOTHER'S AGE YR.	TEST TIME MIN.	SEX OF INFANT	INFANT'S AGE HOURS	TEST TIME MIN.	2ND DAY TEST MIN.	4TH DAY TEST MIN.	6TH DAY TEST MIN.	8TH DAY TEST MIN.
1	N	33	19.7	m	1	6.0	5.1	4.3	4.6	2.8
2	N	22	17.4	m	8	3.5	4.5	4.5	4.6	5.9
3	w	35	17.0	m	6	4.1	7.3*	3.9*	7.4*	
4	w	30	17.0	f	0	4.2	4.3	5.3	4.6	3.7
5	N	20	14.8	m	4	4.3	4.6	3.8	7.4	
6	N	27	14.8	f	0	4.3	6.8	5.4	4.6	
7	w	20	14.4	f†	1	4.0	3.3*	3.4*	5.3*	4.2*
8	LN‡	37	14.2	m	3	6.4	5.3	5.3	5.2	4.1
9	w	27	13.4	m	7	5.7	5.3*	4.1	4.5	4.8
10	w	20	13.4	m	6	4.7	5.2	4.8	8.4	4.3
11	w	29	12.9	m	1	5.4	3.4	5.3	4.0	
12	w	18	12.5	m	9	4.4	7.3*	5.3*	5.4*	8.3*
13	w	20	12.5	m	12	6.1	4.2*	4.0	5.9	4.0
14	LN‡	21	12.3	f	5	7.1	5.4	4.4	4.9	5.9
15	w	23	12.1	f	10	4.5	3.9*	4.6*	4.6*	4.1*
16	w	25	12.1	f	5	7.6	3.9*	4.6*	4.6*	4.1
17	w	21	12.0	f	1	3.3	3.4	5.5	3.4	4.0
18	w	17	11.8	f	7	5.1	6.9*	5.5	4.6	3.3
19	w	25	11.8	m	4	5.3	6.8*	4.9*	4.3*	4.0*
20	w	30	11.3	m	7	5.8	Died 2nd day (heart)			
21	N	19	11.3	m	4	6.1	7.1*	6.9*	5.9	5.3
22	N	21	11.3	m	12	6.3	3.8	4.1	3.3	
23	w	27	11.3	f	0	7.0	3.7*	5.5*	3.5	
24	w	24	11.2	m	2	7.1	4.6	5.5	3.0	6.0
25	w	26	11.2	f	6	7.6	4.0*	5.0*	5.9*	3.9*
26	LN‡	35	11.1	f	1	6.9	4.8	6.3	6.7	
27	w	21	11.0	m	7	4.2	2.6*	4.1*	4.0*	2.9*
28	w	30	10.6	f	8	8.3	5.2*	7.1	5.8	
29	w	21	10.5	m	1	3.2	3.7	4.5	3.4	4.4
30	w	22	10.5	f	4	3.3	3.3*	2.6*	4.2	
31	LN‡	19	10.1	f	1	5.6	3.4*	7.7*	5.0	4.9
32	w	39	10.1	f	9	5.7*	8.0*	4.7	5.5	5.2
33	w	26	9.9	f	5	5.4	3.7	5.1	3.8	4.5
34	LN‡	36	9.2	m	12	3.4	4.0*	4.3*	4.7*	4.7
35	w	28	9.2	f	3	4.1	4.1	3.8	9.1	5.3
36	w	35	9.1	f	5	3.8	3.4	3.9	4.4	
37	N	14	9.1	f	6	3.8	3.5	3.7	3.9*	3.9
38	w	20	9.0	f	4	5.1	3.0*	9.9*	6.3*	4.2
39	w	22	9.0	m	1	4.7	6.6*	5.2*	3.5*	
40	w	34	8.9	f	5	4.5	4.3	5.9	7.2	
41	w	25	8.9	m	1	4.7	3.5	3.8	3.4	3.6
42	w	21	8.9	m	12	5.8	6.1	4.8	4.0	
43	w	39	8.6	f	8	5.7	4.3	4.0	4.4	
44	w	26	8.6	f	4	5.2	4.3	4.2	3.8	
45	LN‡	21	8.5	f	7	4.7	5.7*	7.2	6.1	2.6
46	w	34	8.5	f	8	3.4	4.4	4.7	4.7	
47	w	33	8.3	m	7	3.3	4.9*	4.8*	3.0*	2.9
48	w	25	8.3	f	11	5.3	3.7*	4.0*	5.5*	5.1*
49	LN‡	24	8.2	m	10	5.1	4.7	4.5	4.4	
50	w	23	8.2	f	2	4.1	4.0	4.3	3.1	
51	w	25	8.0	f	8	4.8	5.7	6.0	3.2	
52	w	34	7.8	m	5	3.1	7.0	4.9	5.5	
53	w	18	7.8	m	6	4.8	4.5	3.1	3.2	6.9
54	w	27	7.7	m	5	4.2	4.8	4.6	6.5	
55	LN‡	18	7.7	m	2	4.4	3.3*	3.5	3.3	
56	LN‡	28	7.5	m	2	5.1	4.4	3.8	5.4	
57	w	38	7.5	f†	11	9.5	7.3*	5.7*	4.1	
58	w	20	7.5	f	3	4.7	5.7	6.3*	4.2	5.6*
59	w	35	7.4	m	8	4.3	3.5*	5.0*	4.2	
60	N	21	7.3	f	2	3.6	4.2	4.9	5.0	
61	w	27	7.2	f	2	6.1	4.9*	7.1*	4.8	5.2
62	w	21	7.1	m	2	4.5	4.2	5.7	5.3	
63	w	23	7.1	m	0	3.3	8.1	4.8	5.2	5.0

TABLE I—CONT'D

CASE	RACE	MOTHER'S AGE YR.	TEST TIME MIN.	SEX OF INFANT	INFANT'S AGE HOURS	TEST TIME MIN.	2ND DAY TEST MIN.	4TH DAY TEST MIN.	6TH DAY TEST MIN.	8TH DAY TEST MIN.
64	w	33	6.8	m	5	3.7	6.2	4.5	3.1	5.3
65	w	26	6.7	f	7	3.0	3.9*	4.5*	4.9	4.3
66	LN‡	19	6.5	m	2	3.6	4.2	6.0	4.4	
67	w	22	6.5	f	9	3.3	6.5	3.6*	4.1	
68	w	21	6.5	f	10	4.5	4.4*	5.1	4.5	
69	w	25	6.1	f	7	6.8	4.6	5.7		
70	w	21	6.0	m	10	6.2	4.2	5.7		
71	w	33	6.0	m	1	6.4	5.8	4.8	4.1	
72	w	20	5.9	f	4	5.9	4.6*	6.9*	3.9*	5.7*
73	N	19	5.9	m	5	12.0	3.9	7.1	4.8	4.4
74	w	25	5.8	f	7	4.4	5.9	4.0	4.6	
75	LN‡	22	5.6	f	11	4.3	4.6	4.6	4.7	4.5
76	w	23	5.3	m	9	3.5	4.6*	2.7*	4.6*	5.0*
77	w	44	5.2	f	6	4.2	3.6*	3.4*	4.7	3.2

*Jaundiced.
†Eight months' premature.
‡Light Negro.

that is between 4 and 7 minutes. This was true even in the infants of ten mothers whose skin test time was over 13 minutes (definite tissue unsaturation).

COMMENT

The intradermal test for vitamin C indicates the same maternal-newborn infant relationship as the plasma ascorbic acid levels. The infant tends toward saturation regardless of the mother's tissue concentration. Even where the mother was somewhat depleted, the infant's tissue vitamin C was good. For example, in Case 1, the mother's intradermal test time for disappearance was 19.7 minutes and the infant's was 6 minutes.

The intradermal tests in the infant on subsequent days for a week or more after birth remained approximately the same. The high vitamin C levels are thus not temporary phenomena after birth, but remain constant. In a later report, we shall show how long these vitamin C levels remain high in the infant.

It is difficult to explain how these newborn infants invariably achieve excellent vitamin C nutrition even when the mothers are depleted. There have been several interesting suggestions. Giroud and associates[4] believed that the fetus had the ability to synthesize vitamin C. King[5] thought it was on "the basis of selective conservation of the vitamin in the more vital tissues, such as the pituitary body, during a period of general body depletion." Manahan and Eastman[1c] suggested that there was a selective filtration of vitamin C through the placenta. Lund and Kimble[1c] have presented good evidence that the placenta acts selectively to retain the vitamin C in the fetus. The entire answer cannot be given and may await working out of such things as nervous-hormonal-vitamin relationships.

This raises the question whether other vitamins act in a similar fashion. It is of interest to mention that in an unreported work that we did several years ago, the thiamine blood values were higher in the newborn infant than in the

mother. Thiamine blood values tend to be more nearly stable than those of ascorbic acid. This suggested that the newborn infant also takes its supply of vitamin B_1 even if it must deplete the mother.

CONCLUSIONS

1. A comparison of the vitamin C in seventy-seven mothers and their newborn infants was made by the intradermal test.

2. The vitamin C intradermal test times for disappearance of the dye were always considerably shorter in the newborn infant than in the mother. These results are in agreement with reports of maternal-neonatal plasma ascorbic acid levels.

3. The newborn infant tends toward vitamin C saturation even if it must deplete the mother.

4. Other vitamins, such as thiamine, may act in a similar fashion.

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DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY

V. Staphylococcal Empyema: The Importance of Pyopneumothorax as a Complication

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STAPHYLOCOCCAL infections of the lungs and pleurae merit the particular attention of the pediatrician because of the marked preponderance of such cases in very young children, the difficulties involved in proper treatment, and the high mortality rate. Many older writers did not separate cases of empyema into etiological groups, and it is not until recent years that the unusual features of the staphylococcus as a cause of empyema have been emphasized. The advent of sulfanomide chemotherapy defined the differences between staphylococcal and other types of lung infections more clearly; and now that a more potent antistaphylococcal agent is available, these differences should not be neglected. We wish to emphasize particularly one aspect of staphylococcal empyema—that is, *pyopneumothorax,* or the tendency for air as well as pus to collect in the pleural cavity. This complication occurred with sufficient frequency in our series to warrant its incorporation as a basic feature of the disease. Moreover, it is of sufficient prognostic importance to justify a thorough understanding of methods of diagnosis and treatment.

This paper is a review of the forty-two cases of acute staphylococcal empyema seen at the St. Louis Children's Hospital over the ten-year period from 1934 to 1943, inclusive. This series does not include cases of empyema which developed during the course of staphylococcal sepsis, nor those chronic cases which were admitted for the purpose of obtaining adequate drainage. Cases of empyema following aspiration of a foreign body or those subsequent to surgical lobectomy or pneumonectomy are also omitted. None of the patients received penicillin. With these exceptions, all cases seen during this ten-year period are included regardless of whether or not surgical drainage was used.

The details of the surgical management of these cases were carried out by the Chest Service of the Department of Surgery, under the supervision of Dr. Evarts Graham.

As soon as a sufficient number of penicillin-treated cases have been observed, they will be reported separately.

The Importance of the Staphylococcus in the Causation of Empyema.—The relative frequencies with which the pneumococcus, the hemolytic streptococcus, and the staphylococcus were a cause of empyema at the St. Louis Children's Hospital during the past ten years is shown in Fig. 1. Beginning in 1939, when sulfapyridine first came into wide use, the yearly incidence of pneumococcal empyema diminished promptly, where as the incidence of staphy-

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lococcal empyema actually increased. The peak incidences for the latter indicated for the years 1940 and 1942 are due in part, we believe, to rather widespread epidemics of staphylococcal respiratory infections in the newborn nurseries of St. Louis.

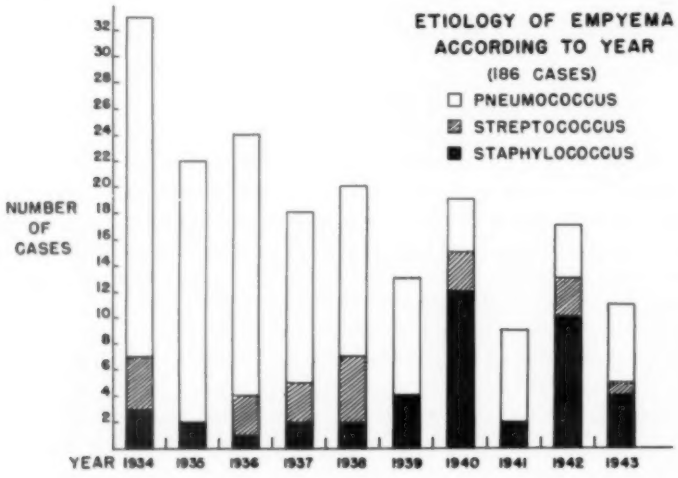

Fig. 1.

Table I is a compilation of data taken from available reports in the literature as to the relative frequency with which the staphylococcus is a cause of empyema in children. Those reports were included which were representative of the pediatric age group as a whole and which gave definite statements as to the causative organism. Papers which dealt exclusively with restricted age groups, with autopsy material, or with surgically treated patients only were omitted, for the purpose of the compilation was to give a picture of empyema from a purely etiological viewpoint as the pediatrician sees it.

Age Incidence.—The influence of age as a factor in the determination of the relative importance of the staphylococcus in the causation of empyema is

TABLE I. INCIDENCE OF STAPHYLOCOCCAL EMPYEMA IN CHILDREN

AUTHOR	DATE	TOTAL CASES	STAPH. CASES	PER CENT STAPH.
Spence,[1] N. Y. C. (Babies Hospital)	1913-1920	204	32	15.0
McNeil and associates,[2] Edinburgh	1929	89	2	2.1
McEachern,[3] Winnipeg	1933	75	6	8.0
McEnery and Brennemann,[4] Chicago	1928-1932	168	14	8.3
Hochberg and Kramer,[5] Brooklyn	1929-1936	255	33	12.9
Neuhof and Berck,[6] N. Y. C. (Mt. Sinai)	1928-1932	182	31	17.0
Benson and Penberthy,[7] Detroit	1926-1941	144	9	6.2
Hurwitz and Stephens,[8] San Francisco	1931-1938	60	8	13.3
Lanman and Dimmler,[9] Boston	1919-1939	467	42	9.0
Ellenberg and Martin,[10] N. Y. C.	1930-1940	115	8	6.9
Riley,[11] N. Y. C. (Babies Hospital)	1922-1943	204	22	10.8
Totals		1963	207	10.5
St. Louis Children's Hospital	1934-1938	117	10	8.5
St. Louis Children's Hospital	1939-1943	69	32	46.4

evident from a comparison of Tables I and II. While many reports in the literature include infants under one year of age, there were only three in which it was possible to clearly determine the incidence of staphylococcal empyema in that age group. Table II presents data which indicate that the staphylococcus accounts for about one-half of all empyema cases in infants under one year of age, as contrasted to 10 per cent for the entire pediatric age group.

TABLE II. INCIDENCE OF STAPHYLOCOCCAL EMPYEMA IN INFANTS UNDER ONE YEAR OF AGE

AUTHOR	DATE	TOTAL CASES	STAPH. CASES	PER CENT STAPH.
Spence,[1] N. Y. C.	1913-1920	53	10	18.9
Neuhof and Berck,[6] N. Y. C.	1928-1932	21	15	17.4
Hochberg and Kramer,[5] Brooklyn	1929-1936	35	14	40.0
St. Louis Children's Hospital	1934-1943	37	27	73.0
Totals		146	66	45.2

The age distribution of the cases of pneumococcal, streptococcal, and staphylococcal empyema seen at the St. Louis Children's Hospital throughout the period covered by this report is indicated in Fig. 2. The largest single group of staphylococcal cases occurred in the group under 6 months of age, and five-sixths of the cases were 2 years of age or less. The staphylococcus accounted for 91 per cent of all cases of empyema in infants under 6 months of age, for 45 per cent in all infants under 2 years of age, but for only 6.4 per cent of empyema cases in children 2 years of age and older.

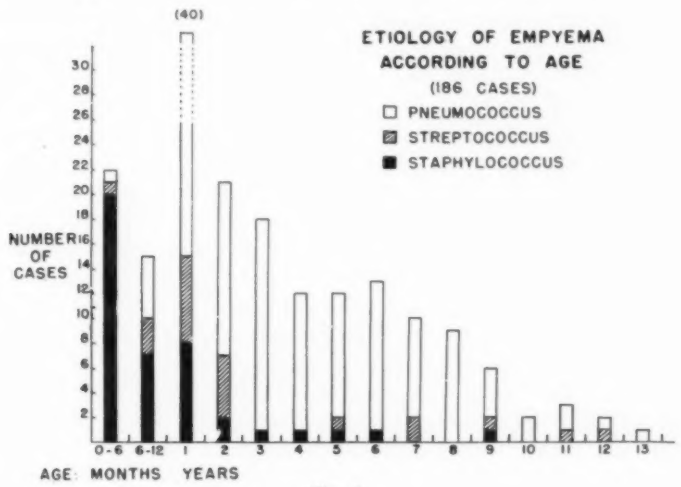

Fig. 2.

Pathologic Considerations.—It is generally agreed that the staphylococcus can cause a true primary pneumonia. Since "primary" empyema, for all practical purposes, does not exist, any discussion of staphylococcal empyema must necessarily include the underlying pneumonic process. The studies of Neuhof and Berck,[6] of Macgregor,[12] and of Kanof, Kramer, and Carnes[13]

present the subject adequately. Staphylococcal pneumonia may produce overwhelming toxicity, to a degree that the patient succumbs in a day or two. Under such circumstances the lungs present one or more areas of massive consolidation which are intensely hemorrhagic in appearance. There are suppleural hemorrhages, and a serofibrinous pleural effusion is usually present. There is evidence of early suppuration, particularly of the bronchial walls and adjacent alveolar tissue, and there may or may not be a generalized bronchitis. Clumps of staphylococci are found in the affected areas. Later in the course of the disease, the areas of consolidation undergo definite suppuration, and one or more abscesses form, empyema resulting upon rupture of an abscess through the pleura. Because of the early involvement of the bronchial walls, and because the abscesses so often ramify, small bronchopleural fistulae are frequently formed, whereupon air enters the pleural space and pyopneumothorax is produced. This can occur at any time during the course of the empyema and may be repeated one or more times as successive abscesses create bronchopleural communications. It is because of the method of pleural involvement that pyopneumothorax occurs more commonly in staphylococcal than in pneumococcal or streptococcal pulmonary infections.

The sequence of events is described well by Neuhof and Berck[6]:

> "The pathologic process in the pleura depends on the site of the pulmonary focus, its extent and the rate of destruction of the overlying parenchyma. In adults the pleural involvement is usually slow and benign. The empyema or pyopneumothorax develops gradually in encapsulated form. Bronchial communications, when present, are generally insignificant, indicating that the abscess in the lung was probably small and subpleural . . . . The collection of pus is in two pockets, with a shelf of infiltrated lung bearing the perforated or non-perforated parenchymal focus lying between them . . . .
>
> "The slow evolution of empyema or pyopneumothorax which has been described as the adult form is also encountered in children. It is not typical of childhood, however, and it is less and less frequently seen as the earliest years of life are approached. *The characteristic lesion in childhood, and more particularly in infancy, is wide rupture of a staphylococcic abscess of the lung into the pleural cavity.** When it evolves slowly, permitting walling-off adhesions to form, pyopneumothorax with little or no displacement of the mediastinum is the result. *On the other hand, total pyopneumothorax with great shift of and tension on the mediastinum occurs when the abscess develops rapidly with early rupture.** Never present in adults in our series, this picture occurred in one-third of the children and in almost all the infants."

Thus, the staphylococcal pneumonic process distinguishes itself from the other common types of pneumonia in two respects: Empyema is a very frequent sequel, and due to the manner in which the empyema is produced pyopneumothorax can often occur.

*Italics are ours.

Clinical and Roentgenographic Aspects.—The onset of the underlying staphylococcal pneumonia in our series of cases was usually gradual: The child had an upper respiratory infection with coryza for several days, followed by fever, cough, rapid respirations, anorexia and listlessness; soon a rather sudden turn for the worse was experienced. The patient rapidly became cyanotic and dyspneic and appeared markedly toxemic. In addition to a typical pneumonic picture, many of the young infants exhibited diarrhea and abdominal distention, the latter to a degree more marked than is usually seen in pneumococcal pneumonia.

In several children the course was fulminating, and the entire chain of symptoms required only twenty-four to forty-eight hours to develop. In some, abdominal distention or abdominal pain together with fever were the presenting symptoms. The dirty, salmon-pink sputum, apparently so typical of staphylococcal pneumonia in the adult, was noted in only one of our patients, an older child. Febrile convulsions occurred in two patients. High fever was a common but not constant feature, especially in the younger infants. Nine patients had admission temperatures between 38° and 39° C., while eight, all under one year of age, had no elevation of temperature on admission to the hospital. The majority of the patients exhibited the usual signs of toxemia: prostration, acute distress, pallor, and the appearances of overwhelming infection. Definite leukocytosis (14,000 to 41,000) occurred in thirty-eight patients, the great majority of whom displayed a definite shift to the left in the Schilling differential count. The remaining four patients had normal or low total white cell counts with marked shifts to the left in the Schilling hemogram; all of these died. Bacteriemia was present in 38.2 per cent of the thirty-four cases in which blood cultures are recorded. The incidence was definitely higher in those patients under 2 years of age (41.4 per cent) as contrasted to children over 2 years of age (20 per cent). Throat cultures were rather inconclusive in this series; they were recorded in twenty-seven cases, and staphylococci were recovered in fourteen of these but were listed as the predominating organism in only seven. In several cases pure cultures of either pneumococci or hemolytic streptococci were recorded.

The physical signs in the chest may be misleading in the young infant. Breath sounds and râles may be heard quite well through an area of empyema fluid despite a dull or flat percussion note. The most suggestive physical finding is the presence of signs of pneumonic involvement of an entire lung field, for empyema will be found in most of the infants who exhibit such findings. In several patients, the physical signs on admission to the hospital were those of massive pneumothorax, the existence of empyema being proved later by diagnostic thoracentesis. When the pneumothorax was limited to a small portion of the lung surface, however, physical signs of it were usually absent.

Fluoroscopic or roentgenographic examination is the only way to arrive at an accurate diagnosis in infants. In uncomplicated staphylococcal empyema, the picture is identical with that of empyema due to other organisms with the exception that the effusion is more frequently seen to occupy an entire lung field. The roentgenographic appearance of pyopneumothorax, however, merits

particular attention. Several characteristic roentgenograms are presented in a subsequent section; unfortunately, due to the critical condition of some of the patients, it was not always possible to obtain roentgenograms at the time pyopneumothorax was most extensive. A large collection of fluid and air with immobility of the corresponding leaf of the diaphragm and a rather

Fig. 3.

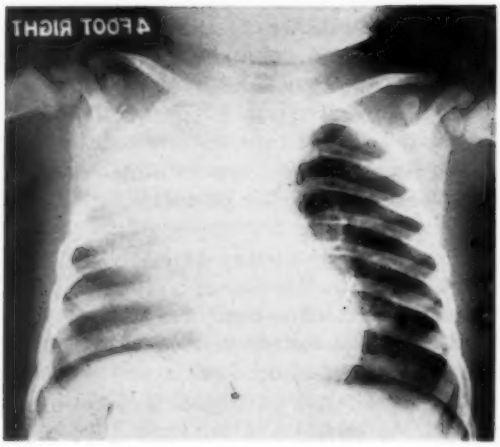

Fig. 4.

marked displacement of the mediastinum are characteristic findings. The pocket of fluid and air may be rather small, however, if the pyopneumothorax developed late in the disease and was limited by preformed adhesions, or several such pockets may be seen arranged in such a manner as to suggest congenital cystic disease of the lung. The important fact to remember is that

the presence of air and fluid in the pleural space of an infant should immediately suggest staphylococcal disease of the lung.

Now that more potent antistaphylococcal agents are available, the diagnosis of staphylococcal pneumonia should be made early in the course of the disease in order to avert, if possible, the occurrence of empyema. The clinical signs in staphylococcal pneumonia, especially in infants, differ but little from those of pneumococcal pneumonia, and the patient's course during the first day or two of the disease usually offers no unmistakable clue. As previously mentioned, throat cultures are not reliable in small children. The finding of staphylococci in the blood stream and the lack of clinical response to adequate sulfonamide chemotherapy were the main criteria used in this series in the diagnosis of staphylococcal pneumonia. Figs. 3 and 4 show roentgenograms of patients with staphylococcal pneumonia. The areas of consolidation are perhaps a little more extensive and somewhat less well-defined than those ordinarily seen in pneumococcus lobar pneumonia, but the character of the lung shadow is far from pathognomonic.

THE IMPORTANCE OF PYOPNEUMOTHORAX

We feel that this extremely important aspect of staphylococcal lung disease has not received the attention it deserves. Isolated case reports of pyopneumothorax occur from time to time in the literature, especially that from England; the majority of these cases ended fatally. There are several large series of empyema cases reported,[1, 5, 9, 10, 11] which include no mention whatsoever of pyopneumothorax; in others[7, 13, 14] it is mentioned briefly but not discussed. McEnery and Brennemann[4] state that "the so-called 'tension-pneumothorax' must be relieved promptly by some continuous method of drainage, or removal of air." The recent report of Clemens and Weens,[15] in which four of the six infants in their series developed pyopneumothorax and manifested striking symptoms as a result of this complication, emphasized the importance of this aspect of staphylococcal empyema. Of the several reports which discuss the problem of pyopneumothorax, both in regard to its seriousness and its proper management, those of Neuhof and Berck,[6] Johnson,[16] and Cohen[17] are noteworthy.

From a consideration of the pathogenesis of pyopneumothorax, which is essentially the result of rupture of a lung abscess into the pleural cavity, thereby allowing air as well as pus to enter, it is evident that the intrapleural air may be present under varying degrees of tension. If the lung abscess develops early and produces a relatively wide pleural rupture, and consequently a large bronchopleural communication, then a massive tension pneumothorax may develop. Under such circumstances the patient always has severe respiratory embarrassment, and sudden death may result. If the pleural rupture is small and occurs later in the course of the pneumonia, the pneumothorax may be limited in extent, due to the existence of pleural adhesions, and only mild symptoms will be produced; or several pulmonary abscesses may rupture through the pleura in succession and thus produce increasing respiratory distress over a period of days. It must be remembered that the less extensive types of pyopneumothorax may at any time, and with alarming rapidity, pro-

gress to the massive tension variety. It should be stressed, then, that every case of staphylococcal lung infection is a potential case of pyopneumothorax, and further, that every instance of pyopneumothorax constitutes a serious danger to the patient.

Pyopneumothorax was definitely demonstrated in seventeen of our patients. This represents a case incidence of 40.5 per cent; thus two of every five patients developed this complication. The age of the patient did not alter the frequency with which pyopneumothorax occurred, the incidence being 40 per cent in children under 2 years of age and 43 per cent in those over 2. These cases represent instances of spontaneous pyopneumothorax only. Air is often introduced purposefully into the pleural space to aid in outlining the empyema cavity, or enters inadvertently during a thoracentesis; under such circumstances no symptoms result.

In our series, four of the seventeen patients with pyopneumothorax exhibited no characteristic symptoms attributable to this complication, the diagnosis being made either by x-ray examination or by noting a rush of air from the pleural cavity at time of surgical drainage.

Three patients had moderate respiratory distress, consisting of dyspnea, rapid respirations, and in one instance cyanosis. Thoracentesis resulted in marked relief of symptoms in two of these patients, and subsequent surgical drainage effected a complete cure. In the other, thoracotomy was done immediately following diagnosis of the pyopneumothorax. Air and pus gushed out under considerable pressure, the patient experiencing immediate relief.

In order to illustrate the symptomatology and proper handling of patients with more marked degrees of tension pyopneumothorax, the remaining ten patients will be discussed individually. All had severe degrees of respiratory embarrassment. Five deaths occurred in this group, and in one instance this complication was the immediate cause of death. In the other four, death was due chiefly to the toxemia produced by the underlying staphylococcal pneumonia; however, pyopneumothorax was a major contributory factor in the death of at least one of these.

CASE REPORTS

CASE 1.—R. O., a 1-year-old white male, was admitted on March 9, 1942. He had had a mild upper respiratory infection for the previous week, and on the day of entry he vomited twice and became feverish and irritable. He was seen in the emergency room, his condition was diagnosed as acute pharyngitis, and he was sent home on sulfadiazine medication. Fluoroscopic examination of the chest was negative at that time. Approximately twelve hours later, following two generalized convulsions, the child was returned to the hospital. Examination of the chest now revealed an area of percussion dullness and bronchial breathing at the right base, and a definite shadow could be seen at that area on fluoroscopy. Sputum culture revealed a pneumococcus type IX; blood culture proved sterile, and the spinal fluid was normal.

The baby was given sulfadiazine, but his temperature remained elevated (39.5 to 40.5° C.), and he gradually became dyspneic and rather prostrated during the next three days. Because of the lack of response to chemotherapy, a staphylococcal pneumonia was postulated; skin tests done with the staphylococcus carbohydrate substance were negative, and administration of staphylococcal antiserum* was begun. During an intravenous injec-

*The serum used in this series was a special antistaphylococcal rabbit serum, prepared by the Eli Lilly and Company under the direction of Dr. L. A. Julianelle.

tion of serum, the baby suddenly developed respiratory difficulty and cyanosis, and adrenalin was given without relief. Fluoroscopic examination now revealed a density over the greater part of the right lung field, and a small area of pneumothorax was noticed at the costophrenic angle. Within an hour, the area of pneumothorax had increased to a point where about one-third of the right lung field was involved, a slight shift of the mediastinum was noted, and respiratory difficulty increased to an alarming degree despite the administration of oxygen. A needle was then introduced into the right pleural cavity and intrapleural pressure readings of 0, +2 cm.* obtained. Closed intercostal siphon drainage was immediately begun; considerable amounts of pus and air gushed out, and respiratory relief immediately followed. *Staphylococcus aureus* was cultured from the pus. Pneumothorax did not recur.

Although sulfadiazine therapy was continued, fever and mild dyspnea, due to the underlying pneumonic process, continued for some time, and one episode of otitis media occurred. Rib resection and open drainage was instituted on April 16, 1942. A total of 65 c.c. of staphylococcal antiserum was given over a period of several days, and skin tests done with staphylococcus carbohydrate were definitely positive by April 7, 1942. The baby was discharged after an eleven-week hospital stay, in good general condition, but with the bronchopleural fistula still open.

CASE 2.—R. M., a 5-month-old white male, was admitted on Jan. 30, 1942, with a history of fever and rapid grunting respirations for the preceding four days. On the day of entry, the dyspnea became much worse and two generalized convulsions occurred. At the time of admission his temperature was 40.5° C., and he was pale, prostrated, and extremely dyspneic. The abdomen was quite distended. Movement of the right chest was limited, and

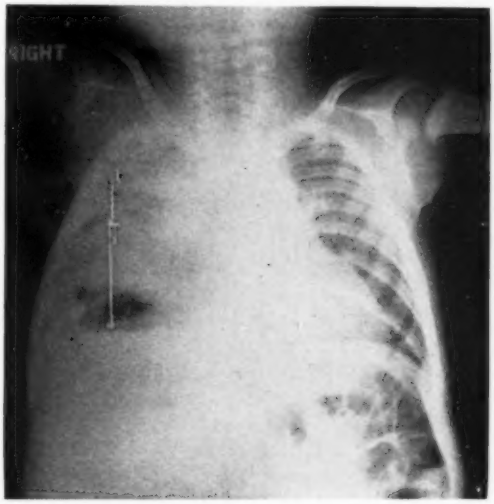

Fig. 5.

there was dullness to percussion over the entire right lung. Tubular breath sounds were heard over the superior portion of the right chest; inferiorly, the breath sounds were suppressed. The chest roentgenogram (Fig. 5) presents the picture of empyema with some shift of the mediastinum, but in addition there are several clear areas to be seen—that is, a pyopneumothorax. Thoracentesis yielded 10 c.c. of thick fluid (positive for *Staph.*

*These and subsequent intrapleural pressure readings refer to centimeters of water, the pressure at the end of inspiration preceding that at the end of expiration.

aureus) and 10 c.c. of air under pressure. Shortly afterward, while a lumbar puncture was being done, the baby went into a state of collapse, the skin became mottled, and respiration practically ceased. Fluoroscopic examination demonstrated a massive right pneumothorax with considerable mediastinal shift. Thoracentesis now produced 80 c.c. of pus and air; an intercostal tube was inserted, and marked relief of symptoms occurred. Closed siphon drainage was maintained until Feb. 16, 1942, when a rib resection was done. Additional treatment consisted of sulfadiazine and supportive measures.

The baby's temperature remained elevated for the first two weeks, but his hospital course was quite favorable, and he was discharged after a stay of eight weeks with the bronchopleural fistula closed.

CASE 3.—S. S., a 4-month-old white female, was admitted on Jan. 5, 1943. She had been hospitalized elsewhere since Dec. 26, 1942, with the diagnosis of pneumonia. Despite sulfadiazine medication, her symptoms had continued, and she had developed a pleural effusion from which the *Staph. aureus* was cultured. On Jan. 2, 1943, fluid and air were removed from the right pleural cavity. On admission to the St. Louis Children's Hospital her temperature was 38.8° C.; she was acutely ill, quite cyanotic and coughing constantly, and there was cellulitis of the right chest wall. There were a flat percussion note and diminished breath sounds over the entire right lung field.

Cyanosis continued despite therapy with oxygen and sulfapyrazine. She remained in a very critical condition, and her respiratory difficulty and cyanosis gradually increased to the point where she was moribund. On the second hospital day a thoracotomy was done with the release of 100 c.c. of pus and air under great tension, and closed siphon drainage was instituted. Immediate and marked relief resulted from this procedure, and her general condition at once began to improve. Open drainage was instituted on Jan. 18, 1943. She was discharged after a hospital stay of four weeks in good general condition and with the chest wound healed.

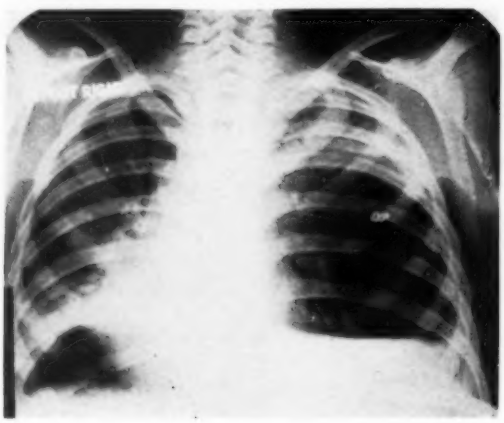

Fig. 6.

CASE 4.—F. M., a 9-year-old white male, was admitted on Aug. 2, 1943. During the preceding month he had been successfully treated at another hospital for mastoiditis, lateral sinus phlebitis, and meningitis due to the *Bacillus proteus*. Shortly before he was transferred to the St. Louis Children's Hospital, he had a recurrence of fever, and signs of pneumonia developed in the left chest. A pleural effusion developed, and 400 c.c. of purulent fluid were obtained from the left pleural cavity. Culture of this fluid revealed *Staph. aureus*.

On admission his temperature was 38.5° C. He appeared chronically ill, apprehensive, and markedly dyspneic, and used his accessory respiratory muscles to the fullest degree. The breath sounds were diminished over the entire left lung field, but except for some percussion dullness at the left base, the remainder of the left chest was hyperresonant. The intrapleural pressure readings were 0, +12 cm. Closed intercostal siphon drainage was begun. A chest roentgenogram the following day (Fig. 6) shows the character of the pyopneumothorax in this patient. It should be noted that the process is bilateral. Obviously, the drainage tube was not functioning properly, so it was reinserted in a higher interspace with the release of a large amount of pus and air from the chest, and for the first time a definite improvement in respiratory symptoms was noted. On the third hospital day a thoracentesis on the right produced a few cubic centimeters of pus, and closed intercostal drainage was also begun on that side. *Staph. aureus* was cultured from the pleural fluid. Once surgical drainage was well established, his general condition began to improve. Additional therapy consisted of sulfapyrazine and blood transfusions. Open drainage was begun on Aug. 12, 1943, and by Sept. 9, 1943, both thoracotomy sites were healed. At the time of discharge on Oct. 30, 1943, both lungs appeared normal on fluoroscopic examination; he was gaining weight and was in good general condition.

CASE 5.—J. O., a 5-month-old white female, was admitted on July 19, 1940, with a history of having had an upper respiratory infection for four days, followed on the second day by rapid grunting respirations. Her admission temperature was 39.5° C.; she was acutely ill, quite dyspneic, and mildly cyanotic. The entire right chest exhibited percussion dullness and diminished breath sounds to physical examination, and diffuse haziness on fluoroscopy. Therapy with sulfathiazole was begun, and the baby improved slightly during

Fig. 7.

the first three hospital days. However, on the third hospital day, a roentgenogram revealed definite evidence of fluid and air in the chest (Fig. 7) and a slight shift of the mediastinum. A few cubic centimeters of thick pus, from which *Staph. aureus* was cultured, were obtained on thoracentesis. Intercostal drainage done that same day produced considerable air and pus. Closed siphon drainage was converted to open drainage after two days. A definite bronchopleural fistula developed, and the baby's course was quite stormy

for the first ten days. However, she gradually improved; the tube was finally removed, and she was sent home after a five-week hospital stay with a small pleural sinus still present.

She remained well for about a week but then became irritable and began to breathe with noticeable effort. She would lie only on her right side and had recurrent episodes of respiratory distress. On re-entry into the hospital on Sept. 11, 1940, her temperature was normal, and she presented the picture of massive pneumothorax: dyspnea, cyanosis, shift

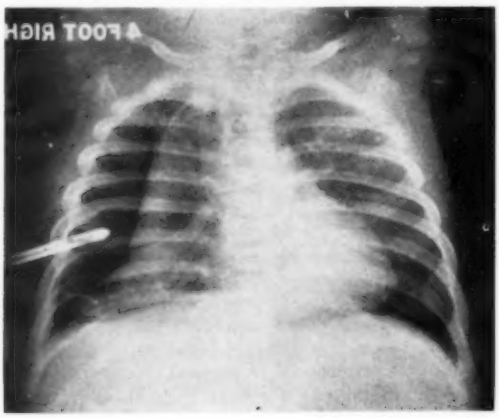

Fig. 8.

of heart and trachea to the left, tympany and diminished breath sounds over the right chest. A needle was immediately inserted into the right pleural cavity and intrapleural pressure readings of +15, +30 cm. obtained. After removal of 800 c.c. of air, the pressures had fallen to −5, +5 cm., and she was considerably relieved. The intrapleural tension rapidly mounted again, however, so closed intercostal siphon drainage was instituted, and large amounts of air bubbled forth constantly from the chest. On the fourth hospital day, she had a recurrence of symptoms, which were relieved promptly by adjusting the tube. A roentgenogram taken at that time is shown in Fig. 8. The picture resembles very closely that seen on fluoroscopy at the time of entry. Very little drainage of pus occurred during this hospital admission. The closed system of drainage was converted to an open one after seventeen days; the bronchopleural fistula gradually closed, and she was discharged home well on Oct. 13, 1940.

These five patients illustrate well the nature of tension pyopneumothorax in children: the rapid onset, the alarming symptoms produced (which often completely overshadow the effects of the staphylococcal infection itself), and the prompt satisfactory response to closed intercostal siphon drainage. The rapidity with which treatment was carried out was life-saving in the first two patients. In the third, treatment was unnecessarily delayed. From her appearance at the time thoracotomy was finally carried out, she certainly could not have survived much longer.

Although pneumothorax was most pronounced in the fourth and fifth patients, it occurred more gradually, and therapy could be carried out with more deliberation, yet their respiratory embarrassment was profound and might well in time have ended fatally. It should be pointed out that the fourth patient was an older child and that he tolerated respiratory difficulties of a degree

that no small infant could. The fifth patient suffered two episodes of pyopneumothorax; pus predominated on the first occasion and air on the second. Respiratory embarrassment was definitely greater on the latter occasion.

There should be no hesitancy about the carrying out of a thoracentesis or a simple thoracotomy for intercostal drainage in patients with tension pyopneumothorax. They are relatively minor procedures which can be done at the patient's bedside without the benefit of elaborate apparatus. No patient's condition should ever be regarded as being sufficiently critical to interdict these live-saving procedures.

CASE 6.—D. H., a 10-month-old white male, was admitted on Dec. 31, 1936, with the history of an upper respiratory infection for the preceding six days. For the last three days there had also been fever and mild dyspnea, and on the morning of admission the child suddenly became cyanotic and extremely dyspneic. The temperature was 39.5° C. on admission; the general picture was that of a cyanotic, critically ill child whose respiratory excursions were limited but who seemed to fight for every breath and was rapidly becoming exhausted. The interspaces on the right were full; the percussion note was tympanitic and the breath sounds greatly depressed over the entire right chest. The breath sounds were of tubular quality on the left. The chest roentgenogram (Fig. 9) shows the extensive right pneumothorax with marked displacement of the mediastinum and an infiltration in the upper right lung field.

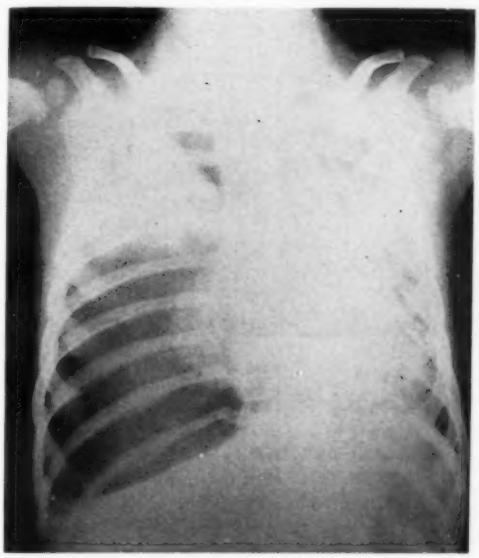

Fig. 9.

Thoracentesis was immediately done. The intrapleural pressure readings were +4, +8 cm., and 300 c.c. of air were easily withdrawn from the right pleural cavity. The patient experienced only temporary relief from this procedure, and the mediastinum remained in its former position, thus indicating that a bronchopleural fistula was present of sufficient size to allow air to enter the pleural cavity rapidly. Closed intercostal siphon drainage was then done, and considerable air bubbled forth from the chest. The child expired an hour later.

At autopsy the right pleural cavity contained 100 c.c. of thin, light greenish fluid from which *Staph. aureus* was cultured. The right upper lobe was congested and was fixed to the

chest wall by a thick layer of fibrinopurulent exudate. It contained four abscesses ranging from 1 to 3 mm. in diameter, the largest of which was connected with the pleural space by a sinus tract approximately 1 mm. in diameter. The right middle and lower lobes were congested and atelectatic. In microscopic section the pleura was covered with a fibrinopurulent exudate, and the sinus tract extending from the pleura into the lung abscess could be identified. The smaller bronchioles were filled with polymorphonuclear leukocytes, and there were scattered foci of alveolar consolidation throughout the upper lobe. The left lung showed changes which were interpreted as evidence of early aspiration pneumonia.

CASE 7.—R. S., a 4-week-old white female, was admitted on June 20, 1938. Two days prior to admission she had become irritable and feverish and had begun to vomit. Her abdomen became distended, and she seemed to suffer some abdominal pain, which was relieved by an enema. On the day of admission, she began to have spells of dyspnea and cyanosis which rapidly increased in severity.

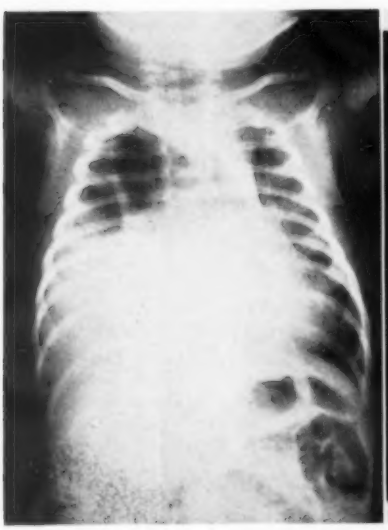

Fig. 10.

Fig. 11.

On admission her temperature was 36.6° C.; she was moribund, cyanotic, and dyspneic. The right side of the chest exhibited fullness of the interspaces and limited respiratory excursions; there was inspiratory retraction of the suprasternal space and of the interspaces on the left. The percussion note over the right posterior chest was flat, and breath sounds were absent over the entire right chest. The abdomen was distended, and the liver edge was felt 4 cm. below the costal margin. The chest roentgenograms (Figs. 10 and 11) show the extensive pyopneumothorax with shift of the mediastinum to the left.

Thoracentesis was immediately performed, and 20 c.c. of pus were withdrawn along with a considerable amount of air under pressure. *Staph. aureus* was cultured from the pus and from the blood culture. The baby experienced some relief from the thoracentesis, and with the help of an oxygen tent her color became normal. Four hours after admission closed intercostal siphon drainage was instituted with return of at least 60 c.c. of thin purulent material and a considerable amount of air. Air continued to bubble forth from the pleural cavity, and the baby did quite well for the first two hospital days. She then began to lose ground, became listless, refused to take feedings, and developed a high fever. Despite continued oxygen and the liberal use of parenteral fluids she expired on the fifth hospital day.

At autopsy there was a thick white fibrinous exudate over the entire right lung, but there were no adhesions between the two pleural surfaces on that side and only a few cubic centimeters of pus in the right pleural cavity. There was a confluent bronchopneumonia of the entire right lung and of the left lower lobe. In the right lung there were two abscess cavities, 1 to 2 cm. in diameter, which had ruptured into the right pleural space. One of these opened onto the diaphragmatic surface of the right lung, and the pus which had escaped from it was completely encapsulated; the other communicated with the open pleural cavity through a jagged opening several millimeters in size. In microscopic section there was extensive consolidation with red cells and mononuclear cells, and numerous clumps of cocci could be seen. Polymorphonuclear cells were not abundant. Except for a large fatty liver, the other post-mortem findings were irrelevant.

CASE 8.— D. Y., a 7-week-old white female was admitted on Dec. 21, 1940. She had been ill for three days with symptoms of fever, slight cyanosis, and dyspnea.

Her admission temperature was 38.0° C.; she appeared critically ill and exhibited rapid shallow respirations, cyanosis, and pallor. The entire right chest was hyperresonant to percussion, and the breath sounds were scarcely audible. A chest roentgenogram revealed several large cystlike areas in the right lung field (Fig. 12).

Fig. 12.

She was given oxygen, which greatly relieved her cyanosis and dyspnea, and sulfathiazole therapy was begun. The following morning a thoracentesis was done and intrapleural pressure readings of 0, +7 cm. obtained. One hundred c.c. of air together with a few cubic centimeters of pus were aspirated. *Staph. aureus* was cultured from the pus. Closed siphon drainage of the chest was immediately begun with resultant improvement in breathing, but she soon became worse, developed hyperpyrexia, and expired the next day.

At autopsy the right pleural surfaces were covered with a thick fibrinopurulent exudate. The right lung contained multiple abscess cavities, one of which communicated with a bronchus and with the pleural cavity by means of a sinus tract about 7 mm. in diameter. Two additional abscesses communicated with the pleura by small sinus tracts, but no bronchial communication could be demonstrated for these. The left upper lobe was covered by a small amount of fibrinopurulent exudate, and there were several foci in the lobe interpreted as early abscesses. There were focal necroses in the liver.

These three cases represent instances in which tension pyopneumothorax produced alarming symptoms; treatment in each case was prompt and effective from the standpoint of the pneumothorax, death coming as a result of the overwhelming toxemia of the infection. The post-mortem findings of multiple abscesses and massive consolidation of the lung indicate the severe nature of the pneumonic process. If penicillin had been available, the latter two of these three children might have recovered.

CASE 9.—J. O., a 3-week-old white female, was admitted on March 10, 1939, after an illness of two days, which began with rhinitis and cough, followed the next day by fever, listlessness, and anorexia. During the preceding week a few small furuncles had been noted on the scalp.

Her admission temperature was 39.2° C.; she was moderately ill and exhibited mild dyspnea, but there was no cyanosis. The lungs were clear to percussion and auscultation, but on fluoroscopy the right middle lobe was seen to be consolidated.

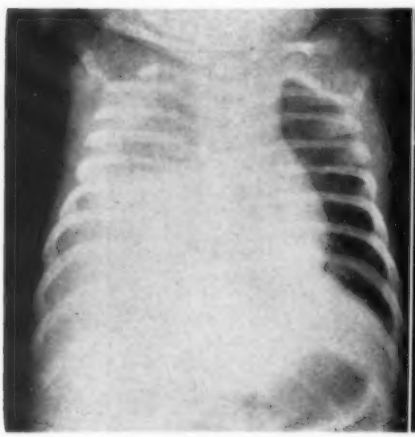

Fig. 13.

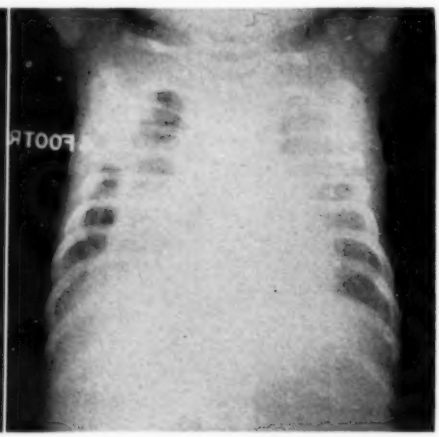

Fig. 14.

The baby was given sulfapyridine and parenteral fluids, but rapidly became worse, and by the next day dyspnea and cyanosis were sufficient to require oxygen therapy. The chest roentgenogram now showed a definite pleural effusion on the right (Fig. 13). By the third hospital day the patient had developed extreme dyspnea, and continued to present symptoms of toxemia despite the fact that her temperature had become normal. The chest roentgenogram at this time (Fig. 14) revealed an extension of the pleural effusion in which there were several small areas of decreased density. On this day she had a sudden episode of apnea and cyanosis, and was revived with considerable difficulty. A similar episode recurred later that day, and because the symptoms were thought to be due to possible brain involvement, a lumbar puncture was done and normal spinal fluid obtained. The right intercostal spaces were noted to be bulging, and on fluoroscopy of the chest an extensive right pneumothorax was discovered, involving about a third of the lung field. Thoracentesis was immediately carried out, but only 7 c.c. of pus and 10 c.c. of air were obtained. *Staph. aureus* was cultured from this pus. The patient expired shortly afterward, just as preparations were being made for surgical drainage. Permission for autopsy was not obtained.

CASE 10.—W. P., a 1-month-old white male, was admitted on Oct. 12, 1939. He had been well until the previous evening, at which time he began to grunt with each respiration

and to cough occasionally. Neither the parents nor the doctor who saw him were particularly concerned about him until three hours before admission. At this time he suddenly threw his head backwards, gasped for breath, and became cyanotic. He sustained two subsequent attacks of a similar nature before admission to the hospital.

On admission his temperature was 38.8° C. He seemed alert and fairly vigorous but was deeply cyanotic and moderately dyspneic. The interspaces of the right chest were full, and on that side the percussion note was tympanitic and the breath sounds distant and suppressed. A chest roentgenogram (Fig. 15) revealed a large pneumothorax on the right and an infiltration in the left upper lobe.

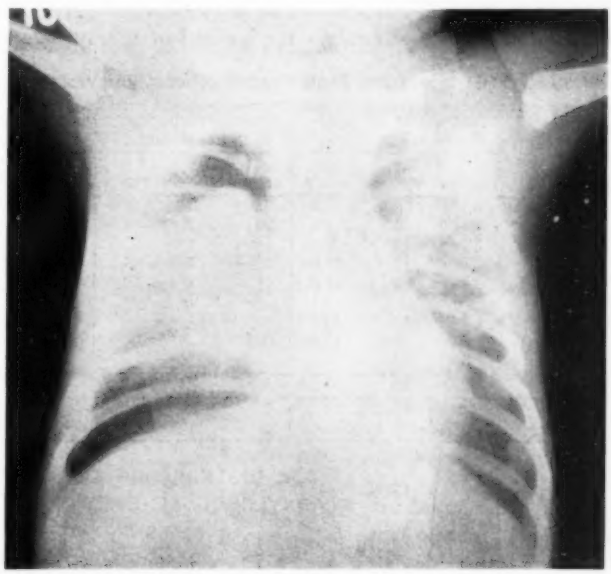

Fig. 15.

The patient was considered to have a spontaneous pneumothorax and was placed in an oxygen tent which gave him considerable relief. Sulfapyridine therapy was begun, and several blood transfusions were given during the next few days. He continued to do fairly well, exhibiting very little fever, until the fifth hospital day. At this time his respiratory rate increased markedly, and evidence of fluid in the right pleural cavity was noticed on fluoroscopic examination. Thirty cubic centimeters of pus (under pressure) were aspirated from the right chest, from which was cultured *Staph. aureus*. Subsequent thoracenteses yielded pus and air, and on the eighth hospital day continuous closed intercostal drainage of the right chest was begun. In spite of these procedures the patient died that same day.

At autopsy the right pleural cavity contained three separate empyema pockets, and there was a fibrinous pericarditis. There was an abscess, 1 cm. in diameter, in the right middle lobe through which there was a sinus tract 1.5 mm. in diameter extending from the pleural cavity to a small bronchus. Microscopic sections revealed an extensive consolidation with mononuclear cells, polymorphonuclear leukocytes, and desquamated epithelial cells enmeshed in organizing fibrin. The bronchioles contained plugs of fibrin and degenerated leukocytes. The pleura was considerably thickened.

These two cases represent the effects of pyopneumothorax in their severest form. In the first, the tension pneumothorax was the immediate cause of death; had thoracentesis been done sooner and had more air been withdrawn from the

chest, the outcome might have been different. In the second, thoracentesis was unfortunately postponed as was surgical drainage, and the pneumothorax contributed appreciably to the fatal outcome.

MORTALITY

Of the forty-two cases in this series, eleven patients died—a case fatality rate of 26.2 per cent. Table III illustrates the experiences of others, as compiled from the literature. Only those reports were included which represented a continued experience with this disease at a given clinic over a number of years. No attempt was made to analyze the method of therapy employed.

TABLE III. MORTALITY FROM STAPHYLOCOCCAL EMPYEMA

AUTHOR	CHILDREN OF ALL AGES			CHILDREN UNDER 1 YEAR OF AGE			CHILDREN UNDER 6 MONTHS OF AGE		
	CASES	DEATHS	PER CENT	CASES	DEATHS	PER CENT	CASES	DEATHS	PER CENT
Ladd and Swan[14]	33	9	27.3	22	8	36.3	12	8	66.7
Riley[11]	29	10	34 5	22	8	50.0	14	5	35.7
Hochberg and Kramer[5]	33	13	40.0	14	7	52.5	11	6	54.5
Neuhof and Berck[6]	31	13	42.0	15	8	66.7			
McEnery and Brennemann[4]	14	6	42.8	6 10	4 5	50.0			
Spence[1]	32	14	44.0						
Hurwitz and Stephens[8]	8	3	37.5						
Farr and Levine[18]	6	4	66.7						
Total	186	72	38.7	89	40	45.0	37	19	51.3
St. Louis Children's Hospital	42	11	26.2	27	11	40.7	20	7	35.0

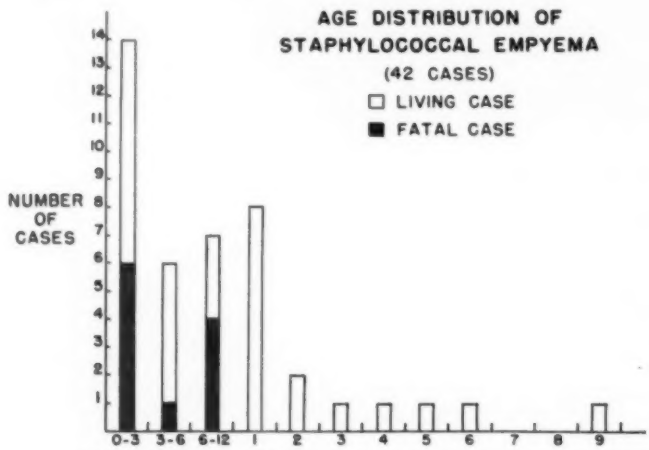

Fig. 16.

It is at once apparent that a factor of great importance in the mortality is the age of the patient. Staphylococcal empyema is not only more common in young infants, but it is also more serious. In our series the case fatality rate as related to age is shown in Fig. 16. In the fourteen infants under 3

TABLE IV. MORTALITY FROM STAPHYLOCOCCAL EMPYEMA BY YEARS

YEAR	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	TOTAL
Total cases	3	2	1	2	2	4	12	2	10	4	42
Deaths	2	1	1	1	1	2	2	0	1	0	11
Mortality rate					60%					15.6%	26.2%
Children under 1 year	2	1	1	1	1	2	8	2	6	3	27
Deaths	2	1	1	1	1	2	2	0	1	0	11
Mortality rate					100%					23.8%	40.7%

months of age, 42.8 per cent died; of the six between 3 and 6 months of age, 16.7 per cent died; between 6 and 12 months of age, 57.1 per cent of the seven infants died, and of the fifteen 1 year or older there were no fatalities.

Table IV presents an analysis on a yearly basis for our series of cases, the entire series being represented in the upper portion of the table, and those cases under 1 year of age in the lower portion.

The division of cases into two five-year periods was not made solely to divide the entire period covered by the series into two equal portions, for in 1939, sulfapyridine, a drug considerably more effective than sulfanilamide against the staphylococcus, came into wide usage. It is seen that whereas the total mortality rate for the first five-year period is 60 per cent, that of the second has been reduced to 15.6 per cent. A similar reduction in mortality in recent years was noted by Riley.[11] In our series it is due to several factors: an increase in the number of cases in recent years has made the house staff more experienced in the diagnosis and general handling of these patients; the more frequent use of the fluoroscope in the examination of infants' chests has led to earlier and more nearly accurate diagnosis; and the importance and dangers of pyopneumothorax have become more widely appreciated. Further, the conclusion that the sulfonamide drugs, given to most of the patients during the latter five-year period, were a definite factor in lowering the mortality cannot be lightly dismissed. Intercurrent streptococcal and pneumococcal infections, so likely to occur in any children's hospital, have certainly been better controlled since the advent of sulfonamide chemotherapy. This factor, together with the known antistaphylococcal effect of the sulfonamide drugs, however small it may be, undoubtedly was a real help to our patients. The general improvement in diagnostic methods can be strikingly illustrated by a comparison of Rienhoff and Davison's[19] series, covering the period from 1889 to 1927, with our own. In the former, twenty of eighty cases, or 25 per cent, were first diagnosed at autopsy while in our series only two of forty-two cases (5 per cent) were unrecognized during life. That this reduction of mortality in our series in recent years is not due to a fortuitous age distribution is borne out in the lower portion of Table IV in which only those cases under one year of age are considered. The same favorable trend is illustrated: a reduction from 100 per cent mortality in the years 1934 to 1938, to 23.8 per cent in the last five years.

Contrary to the statements of Ladd and Swan,[14] we believe that bacteriemia does influence the outcome in cases of staphylococcal empyema. Positive blood

cultures were obtained in thirteen of the thirty-four patients for whom blood cultures are recorded. Six of these thirteen patients, or 46.1 per cent, died as contrasted to a fatality rate of 23.8 per cent for the 21 nonbacteriemic cases.

The principal causes of death in the eleven fatalities which occurred in our series are as follows: Seven patients died of toxemia; in one of these tension pneumothorax was also a major factor; in another the empyema was bilateral and bacteriemia was present. One patient succumbed to a tension pneumothorax. One patient died suddenly following open drainage of the chest; the cause of death here is not known; air embolism and open pneumothorax secondary to open drainage of the chest are two definite possibilities. In two patients, empyema was unrecognized until a postmortem thoracentesis was performed.

TREATMENT

A consideration of these factors points the way toward a logical plan of therapy for infants with staphylococcal empyema.

First, therapy should be directed against the infecting agent. The fulminating course of the disease in some patients may produce death before empyema becomes clinically evident and can be approached surgically. This was the case in two of our patients, the empyema cavity being quite small on post-mortem thoracentesis. If it is possible to treat the patient at the stage in which the pneumonia is still of the hemorrhagic variety and before definite abscesses have formed, the results should be distinctly better, and occasionally an empyema might be aborted. Once lung abscesses are formed, all forms of therapy become much less effective. Of the three agents which are of value in combating the staphylococcus (penicillin, the sulfonamide drugs, and antistaphylococcal serum), penicillin is to be preferred because it has proved itself to be much more powerful than the latter two. At the present time it is our policy to administer penicillin subcutaneously in amounts of 5,000 to 10,000 units every two hours to any small infant with pneumonia who demonstrates one of the following phenomena: (1) failure of response to one of the sulfonamide drugs (exclusive of sulfanilamide) in adequate dosage over a period of twenty-four to forty-eight hours, (2) presence of staphylococcal bacteriemia, (3) a massive pneumonic shadow involving all or the majority of one side of the chest, (4) the occurrence of spontaneous pneumothorax. As the recent experiences of Philips and Kramer[20] indicate, had penicillin been available throughout the period covered by this study, the mortality would most certainly have been lower, and the total duration of the illness shorter.

There are four patients in our series who we feel were definitely benefited by the use of sulfonamide chemotherapy. Definite temperature responses occurred in all four, and they showed a clinical response of moderate degree. Sulfadiazine was employed in two of the cases, sulfathiazole in one, and sulfapyrazine in one. Antistaphylococcal serum was also used in one of these but was given relatively late in the course of the disease at a time when some improvement was already manifest. Striking clinical improvement did not

occur in any case, however, until thoracentesis was done, and eventual cure was effected in each case by thoracentesis alone.

Our conviction that the sulfonamide drugs are occasionally of some value in staphylococcal lung infections is strengthened by the following case, an instance of staphylococcal pneumonia without empyema, in which the patient recovered completely on sulfathiazole medication. This case is not included in the series herein reported because empyema did not develop. The patient, an 8-month-old white female, was admitted to the hospital after an illness of three days and presented typical findings of lobar pneumonia. Sputum and blood cultures were positive for *Staph. aureus*. On sulfathiazole medication the temperature fell by lysis to normal in six days; at that time resolution of the lung shadow was first noted, and the baby showed definite clinical improvement. She was discharged well on the fourteenth hospital day, having shown no evidence of empyema at any time.

From such experiences we feel that sulfonamide chemotherapy does have a definite though quite limited place in the treatment of staphylococcal infections of the lung in children. Of the thirty-four patients in our series who were given one of the sulfonamide drugs, the four mentioned are the only ones, however, in which a clear-cut effect on the staphylococcal infection from such treatment was observed. In the others, symptoms progressed rapidly, and real improvement did not occur until surgical drainage was established.

Antistaphylococcal serum was employed in four patients. The results in this series are largely inconclusive: Two of the patients had extremely prolonged febrile courses following surgical drainage, and the relative role of serum in bringing about eventual recovery may have been appreciable but is impossible to evaluate. One of the other patients was mentioned in the discussion of chemotherapy; the remaining case was that of a small infant who was extremely toxemic and exhibited no fever, and here, too, the effect from serum was inconclusive. All of these patients recovered, but two of them were over one year of age and, therefore, in that group in which the mortality is lowest. From our over-all experience with staphylococcal infection, however, we believe that antistaphylococcal serum might well be beneficial in the small infant (i.e., one whose immune responses might not be adequate) whose course seems unnecessarily prolonged.

Second, general supportive measures are of the greatest importance. The great majority of the patients in this series received one or more blood transfusions. Oxygen was used freely to combat marked dyspnea, cyanosis, and excessive abdominal distention. Parenteral fluids were used frequently to relieve dehydration and to provide food in the form of dextrose, Amigen, and plasma. Once surgical drainage has been established, considerable amounts of protein may be lost from the patient's body through drainage of pus.

Third, surgical drainage is paramount. Symptoms and signs of infection in patients with staphylococcal empyema usually persist until the empyema is drained, whereupon a veritable "crisis" occurs: The temperature and white blood count drop to normal, the patient looks much better, his appetite and

color improve, dyspnea disappears, and oxygen therapy is less often needed. Because of the pathogenesis of staphylococcal empyema, we believe that certain principles are of the greatest importance from the surgical viewpoint: The foremost of these is the avoidance of tension pneumothorax. First, consider every pneumothorax in a young baby to be the result of staphylococcal pulmonary disease until proved otherwise. Second, a diagnostic thoracentesis should be done in every case of pneumonia in which signs of infection persist despite adequate antibiotic or chemotherapy. Third, once the diagnosis of a staphylococcal empyema involving the greater portion or all of that particular pleural space has been established, surgical drainage should be done immediately. Closed intercostal siphon drainage is the method of choice; the procedure is easily and quickly accomplished, is easily withstood by even the most toxemic patient, permits adequate drainage, and, most important of all, obviates the possibility of tension pneumothorax. After a suitable length of time and upon stabilization of the mediastinum, this is converted to open drainage. If a tension pyopneumothorax is present at the time the patient is first seen, thoracentesis should be done with withdrawal of all available air, to be followed immediately by closed siphon drainage to prevent recurrence.

If the empyema proves to be more or less localized by preformed pleural adhesions and is not extensive, then surgical drainage is not as urgent, for if a pyopneumothorax does form, it will often be limited in extent and unable to constitute a threat to the patient's life. The time for and the type of surgical drainage is left to the discretion of the thoracic surgeon in such cases. However, the danger of pyopneumothorax is such a constant one that during the preoperative course the patient should be constantly watched, and a thoracentesis set made immediately available at all times.

No attempt has been made in this series to analyze the type of surgical drainage, for it varied with the status of each patient's particular empyemic process and was highly individualized. While four of our patients recovered by thoracentesis alone, these were the ones whose empyemic processes were limited in extent and in whom the sulfonamide drugs seemed to exhibit a definite beneficial effect. In several patients, in whom empyema had been present for several days before hospitalization and in whom the intrapleural pus was quite thick and tenacious, rib resection and open drainage were done on admission to the hospital, for it was obvious that an intercostal drain would not have provided an adequate outlet for the infected effusion.

Despite the hope that the use of intrapleural and parenteral penicillin might obviate the necessity for surgical drainage in the treatment of empyema —a hope which has been expressed frequently in the recent medical literature— we are convinced that surgical drainage is, and will continue to be, a principle of fundamental importance in the management of patients with staphylococcal empyema. Poppe[21] and Blades and associates[22] point out that even though an empyema cavity may be rendered sterile by intensive penicillin therapy, surgical drainage must still be used to effect eventual cure in the majority of patients.

SUMMARY AND CONCLUSIONS

1. Forty-two cases of staphylococcal empyema observed at the St. Louis Children's Hospital during the past ten years are presented and discussed. The mortality rate for this series, which does not include penicillin-treated cases, is 26.2 per cent.

2. The importance of pyopneumothorax and the frequency with which it occurs are emphasized. This complication occurred in seventeen (40.5 per cent) of our patients; it was a direct cause of death in one patient and contributed in large part to the death of another. Four additional patients experienced alarming symptoms and would have died without prompt and correct treatment. Staphylococcal pyopneumothorax should be seriously considered in the differential diagnosis of spontaneous pneumothorax in young infants.

3. The striking predilection of staphylococcal empyema for young infants and the higher mortality in this group are demonstrated.

4. General supportive measures and surgical drainage constituted the two most important aspects in successful treatment in our series. The use of closed intercostal siphon drainage is advocated as a means of obviating the possibility of tension pyopneumothorax and at the same time providing adequate drainage. The sulfonamide drugs and antistaphylococcal serum were of limited usefulness.

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BILATERAL RENAL AGENESIS

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AMONG approximately 5,000 necropsies on fetuses and newborn infants performed at the Chicago Lying-in Hospital* during the last ten years, 20 infants with complete renal agenesis have been observed. Nine were born in this hospital, six were born at home or in other hospitals, and were sent here for post-mortem examination. Five were examined grossly in other hospitals or mortuaries, and tissues and histories sent here for study. The incidence in the total series of autopsies is 4 per 1,000 dead infants and fetuses. The incidence among deliveries in this hospital is approximately 0.3 per 1,000 births or 7.0 per thousand deaths and stillbirths. The higher incidence among infants born in this hospital is probably due to the inclusion in the total number of autopsies of a disproportionately large number of infants who died in the antepartum period. Renal agenesis is a much less frequent cause of death in fetuses dying before labor than it is in infants who are born alive or who die during labor. These figures are in sharp contrast to the widely accepted belief that complete renal agenesis is a rare condition almost never found except in grossly monstrous infants.

Several reviews have appeared in the last few years in which each author has discussed the cases previously described by other investigators and has added one or two he has personally observed. Rosenbaum,[1] in 1931, combined 32 cases which had been found in the literature by Coen and reported in 1884, with 59 which were subsequently described by other authors and added one of his own. Madison,[2] in 1934, reported 4 cases of his own and found 6 more that had been observed by other investigators. In 1937, Amolsch[3] read all of the previous reports and added 4 more cases bringing the total to 119. In 1939, Soloway[4] reported 2 cases, the only ones observed in the course of 12,000 autopsies at the Cook County Hospital.

In 1940, Hinman[5] was able to find 18 other recorded cases. After adding one of his own, he concluded that 135 authentic cases had been described since 1663. Later that same year Grimm[6] reported the case of another infant which was unusual in contrast to most of those previously reported, in that the absence of kidneys and ureters was the only abnormality. In 1944, Nation[7] reported 3 similar infants found among 27,000 autopsies at the Los Angeles County Hospital. Stokes,[8] also in 1944, described an infant with renal agenesis and multiple internal anomalies.

Among the 119 cases collected by Amolsch in which the descriptions were adequate, there were 81 infants with gross anomalies of the lower limbs. Of these 30 were sirenomelus, 2 apus, 8 monopus, 9 headless monsters with abnormal lower extremities, and 32 exhibited less spectacular disturbances of the lower

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*Only about one-fifth of these infants were born in the Chicago Lying-in Hospital. The remainder were sent to us for study by the courtesy of many physicians and hospitals in the City through the coopeartion of the Chicago Health Department.

limbs. There were 63 males, 24 females, and 32 that were unclassified. Amolsch stated that a dysplasia of the genital system was common in the female and that although the Fallopian tubes were present, the uterus and vagina were ordinarily absent. In 2 cases both adrenal glands were absent and in 4 cases one was absent.

The 20 infants included in the present report exhibit much the same findings as those previously described. The principal difference lies in the proportionably small number who would be considered gross monsters. Four exhibited multiple skeletal abnormalities, but in only one was there the great disturbance in the development of the lower part of the body that results in sirenomelus.

The 19 available maternal histories contain nothing of especial note. Maternal age ranged from 18 to 39 years with the median of 24 years. Nine women were primigravidas; 10 were multigravidas. Two had had previous abortions. Only 2 had had more than 2 preceding pregnancies; one had had 11 children, the other, 7 children and 3 abortions. The method of delivery was unrecorded in 2, spontaneous cephalic 9, breech 6, mid-forceps 1, Cesarean section 1, and craniotomy 1. Nineteen of the mothers were white; 1 was Negro.

An attempt to ascertain the amount of amniotic fluid was disappointing. In no instance was it possible to obtain a definite history of rupture of the amniotic sac. In no case were the membranes ruptured artificially prior to or during labor. In no case was an absence of amniotic fluid mentioned and it seems to have been universally taken for granted that the fluid must have escaped prior to hospital admission. In one instance the physician reported that the infant's body was so unusually dry that he encountered some difficulty in extracting it. There is, therefore, no conclusive evidence concerning the amount of amniotic fluid. The fact, however, that (as far as can be determined) no fluid was observed by any of the obstetricians seems to warrant the conclusion that in the majority of cases it was probably reduced in amount. If more definite information concerning the amniotic fluid had been available it might have been possible to shed some light on the importance of secretion by the fetal kidneys in maintaining a normal volume of amniotic fluid. It can be definitely stated, however, that kidney function is not necessary for the maintenance of intrauterine life.

Fetal death occurred prior to the onset of labor in 1 instance, during labor in 6, and after birth in 13. The length of life varied from 25 minutes, to 11 hours and 15 minutes, with a median of 1 hour and 38 minutes. Weight varied from 700 to 3,000 Gm. with a median of 1,645 Gm. There were 17 male and 3 female infants. This is a more striking tendency toward sex-linking than is found in any other malformation except anencephaly. Over 90 per cent of anencephalic infants are females. Interestingly enough, in spite of the multiplicity of malformations which is found in association with anencephaly, not once has renal agenesis been recorded.

Clinical histories of the infants born alive show nothing remarkable. The majority were cyanotic or breathed with difficulty. In a few, in spite of the fact that the heart continued beating for some time, respiration could not be established.

TABLE I. ASSOCIATED MALFORMATIONS

CASE	MATERNAL AGE (YEARS)	GRAVIDITY	ABORTIONS	METHOD OF DELIVERY	GESTATIONAL AGE AT BIRTH IN WEEKS	LENGTH OF LIFE	CLINICAL CAUSE OF DEATH	SEX	WEIGHT (GRAMS)	LUNG WEIGHT (GRAMS)	LUNG WEIGHT FOR NORMAL INFANT OF SAME SIZE (GRAMS)	FEET AND GENITOURINARY	CARDIAC	ABDOMINAL VISCERA	SKELETAL AND MISCELLANEOUS
1	28	1	0	Sp. ceph.	40	44″	I. C. Hem.	M	2,700	17.0	52				
2	29	2	1	Sp. ceph.	34	11′ 14″	Prem.	M	1,380	19.0	30				
3	22	1	0	Breech	34	2′ 15″	Asphyx.	M	1,655	Hyp.	38				
4	33	3		Ces.	36	2′ 14″	Asphyx.	M	1,980	Hyp.	44				
5	21	2	0	Breech	38	S. B.	Asphyx.	M	1,600	13.3	38				
6	28	3	0	Sp. ceph.	36	1′ 38″	Asphyx.	M	3,000	16.6	55	Clubfeet			
7	30	8	3	Sp. ceph.	35	S. B.	Asphyx.	M	2,000	Hyp.	44	Hypospadias	Aortic atresia		
8	21	1	0	L. F.	38	3′ 8″	Prem.	M	2,330	20.0	47	Clubfeet			
9	18	1	0	Sp. ceph.	26	S. B.	Asphyx.	M	700	3.8	20	Clubfeet			
10	26	2		Sp. ceph.		1′ 1″	Asphyx.	M	2,150	Extr. hyp.	44	Clubfeet	Pulmonary atresia		
11	22	1	0	Sp. ceph.	39	1′ 32″	Asphyx.	M	1,645	12.5	38	Clubfeet		Absent rectum and anus	
12	32	12	0	Sp. ceph.	30	S. B.	Asphyx.	M	1,100	13.0	25			Hypoplastic adrenals	Meningocele, microphthalmia
13										Extr. hyp.		Clubfeet			Hydrocephalus, spina bifida
14	22	1	0	Sp. ceph.	28	S. B.	Malf.	M	1,015	16.0	25 Twin			Imperforate anus	Scoliosis, rib anomalies, short neck, absent radii and thumbs, extra toes

15	23	1	0	Breech	38	S. B.	Malf.	M	800	3.0	20	Twin	Clubfeet			Absent lumbar and sacral spine, rib anomaliès, webbed neck, preauricular nodules, contractures of hips, knees and elbows, hydrocephalus.
16	24	3		Breech	37	30″	Malf.	M	2,365	7.0	47		Clubfeet			Abnormal cervical vertabrae, short neck, contracture of hips and elbows, arthrogryposis of knees
17	21	1	0			2′ 2″	Malf.	M	1,180	9.9	25			Septal defect	Duodenal atresia; malrotation, absent sigmoid, rectum, and anus	Sirenomelus
18	39	3	0	Cran.	37	S. B.	Malf.	F	2,620	13.0	50		Absent vagina and uterus			Hydrocephalus
19	22	3	0	Breech	34	59″	Asphyx.	F	1,580	11.5	33		Absent uterus and vagina		Malrotation of intestine; hypoplastic spleen	
20	24	1	0	Breech		25″	Malf.	F	1,365	17.0	30		Absent uterus and vagina	Double vena cava	Imperforate anus; Meckel's diverticulum	Contractures of elbows and hips, arthrogryposis of knees

Sp. ceph., spontaneous cephalic; Ces., cesarean section; L. F., low forceps; Cran., craniotomy; S. B., stillborn; I. C. Hem., intracranial hemorrhage; Prem., premature; Asphyx., asphyxiation; Malf., malformation; M, male; F, female; Hyp., hypoplastic; Extr. hyp., extreme hypoplasia.

The clinical impression as to the cause of death was: intracranial hemorrhage 1, asphyxia 11, and malformation 8. In the 8 with a diagnosis of malformations, there was hydrocephalus (3), multiple skeletal anomalies (4), and a small meningocele (1). In the others, external malformations were absent (6), limited to clubfeet (4), or to those sufficiently mild to be easily overlooked on superficial examination (2). The various malformations are shown in Table I. Clubfeet were found more commonly than any other associated disturbance, but there were 5 infants with gastrointestinal abnormalities (imperforate anus, 4) and 3 with hydrocephalus. Four of the most malformed infants exhibited a somewhat uniform disturbance consisting of contractures of the hips, elbows, and sometimes the knees, with occasional absence or duplication of bones of the extremities and shortening or webbing of the neck. One infant had an almost complete absence of lower extremities. Both this infant and one with generalized contractures of the extremities, had clubhands associated with absence of the thumb and radius.

Two anomalies were observed in almost all of these infants which to my knowledge have not previously been recognized as characteristically associated with renal agenesis. These are hypoplasia of the lungs and an abnormal facial expression.[8]

In the 14 cases with recorded lung weight, this varied from 15 per cent to 60 per cent of the average lung weight for a normal fetus of corresponding size. In the 7 with unrecorded lung weight, all lungs were stated to have been hypoplastic (Table I).

The histologic appearance of all lungs was similar. The bronchi were prominent and proportionately more numerous than normal because of inadequate parenchymatous development. The alveoli were often rudimentary and in many cases they and the respiratory ducts were lined by cuboidal epithelium. Capillary ingrowth into the alveolar walls seemed to have been greatly inhibited. In almost all instances, the lungs resembled those of a fetus of less gestational age than the one in which they were found.

Anencephalic monsters and infants with diaphragmatic hernias frequently show a somewhat similar pulmonary hypoplasia. In many anencephalic infants, especially those with an associated spinal rachischisis, the thoracic cavity is so reduced in size that the lungs do not have room for normal development. An extreme unilateral hypoplasia is usually found in infants with a diaphragmatic hernia. The presence of abdominal viscera within the thoracic cavity reduces the space available for lung growth; both lungs are almost invariably hypoplastic but the reduction in size and in alveolar development is greater in the lung which is on the same side as the diaphragmatic defect.

In infants with renal aplasia the space within the thorax is normal and the hypoplasia cannot be explained on the basis of inadequate room for expansion. There is no apparent relationship between the embryologic development of the lungs and the ureters and kidneys. The reason for delayed differentiation of pulmonary tissue remains unexplained.

The peculiar facies of these infants likewise seems to have no specific embryologic correlation with the renal anomaly. The face most characteristically exhibits an increased space between the eyes, a prominent fold which arises at the inner canthus and sweeps downward and laterally below the eyes, an unusual flattening of the nose, excessive recession of the chin, and moderate enlargement and decreased chondrification of the ears. The face gives a suggestion of premature senility and is sufficiently characteristic to warrant a diagnosis of coexisting renal aplasia when it is observed.

Fig. 1.—Case 2. Lateral view of head showing large low-lying ears.

An interesting associated anomaly which was present in all 3 of the females in this series and which seems to have been present in practically all of those reported in the literature is the complete failure of development of the part of the Müllerian ducts which ordinarily fuse to become the uterus and vagina; the Fallopian tubes are usually normal.

It appears that whatever agent prevents the outgrowth of the ureteral bud from the Wolffian duct inhibits the caudal extension of the Müllerian duct. The Wolffian ducts are not intrinsically altered and in all of the male fetuses in this series, prostate, seminal vesicles, ductus deferens, and testes were normally formed. The Fallopian tubes and gonads in the three females were normal but, instead of being attached to a uterus, the Fallopian tubes ended blindly and became lost in the suprapubic connective tissue.

In the normal 10 mm. embryo, the Wolffian ducts have already given rise to the ureteral buds and the metanephric blastema has condensed around the terminal portion of the growing ureter to initiate the formation of the definitive kidney. Gruenwald[9] has shown that at about this time each Müllerian duct makes its first appearance as a funnel-shaped invagination of the mesonephric ridge. This lies a short distance from the Wolffian duct and is separated from it by mesenchyme. It grows caudad for a very short distance as a separate structure, but soon is found in intimate contact with the wall of the Wolffian

duct, the Müllerian and Wolffian ducts being surrounded by a common basement membrane. Whether the Müllerian duct grows downward beside the Wolffian duct but within its basement membrane, or whether the Müllerian duct comes into existence by being split off from the Wolffian duct has not been definitely determined. At any rate the contact of the two structures is so intimate that inhibition of the normal development of the Wolffian duct necessarily inhibits normal growth of the Müllerian duct. Gruenwald has shown in chick embryos that if downward growth of the Wolffian duct is interrupted, the Müllerian duct will not extend beyond that point. It seems probable, however, that none of

Fig. 2.—Case 5. Typical facies. The disk-shaped suprarenal glands are visible in the posterior abdominal cavity.

the infants in this series with bilateral renal agenesis suffered complete interruption in the growth of the Wolffian ducts. It would seem that the inhibition of ureteral outgrowth and of Müllerian tube downgrowth must be a very localized process since all but one of the infants had a bladder and urethra and in the males the Wolffian system was normal except for the absence of ureters and kidneys. Another possible, but highly improbable, explanation consists in

the failure of formation or premature atrophy of the cephalic portion of the Wolffian duct including the portion from which the ureter normally arises. Since the Müllerian duct does not descend caudally in the absence of the Wolffian duct the existing portions of Fallopian tubes may have developed completely from the ostial part of the Müllerian duct which arises from the mesonephric ridge independently of the Wolffian system.

In none of the infants in this series was any portion of ureter present. In none was even rudimentary kidney tissue found in any portion of the abdominal cavity. This finding corroborates the belief of other investigators that the differentiation of the metanephric blastema is dependent on the stimulus afforded by the presence of the ureter.

Fig. 3.—Case 19. Typical facies.

The persistence of the bladder as a slender tubelike structure with little musculature in its wall appears to be secondary to the absence of the stimulation for growth normally found in the necessity for a reservoir for kidney secretions.

The suprarenal glands were normal in all but one infant in this series. In this one instance, the glands were of approximately one-half the normal weight. The component parts showed normal relationships and there was no abnormality except the reduction in size. All of the suprarenal glands in the series were round disklike structures placed flat against the posterior abdominal wall. The usual "cocked-hat" shape of the suprarenal is due to the pressure exerted against it by the upper pole of the kidney. When the pressure is nonexistent it remains undistorted and is a smooth circular flat structure.

SUMMARY

Twenty instances of complete renal agenesis have been observed during a ten-year period among approximately 5,000 infants who were subjected to postmortem examination following intrauterine death or death in the neonatal period.

There was no relation to maternal age or parity, method of delivery, or to complications of pregnancy. The infants were predominately males. The three

female infants exhibited a complete absence of uterus and vagina. The lungs of all infants were hypoplastic and the faces of all infants showed a characteristic expression. Prior to post-mortem examination only eight infants were believed to have died because of malformations.

The number of infants observed in this group of necropsies indicates that complete renal agenesis is not as rare as the small number of cases previously reported would indicate.

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LABORATORY AND CLINICAL CRITERIA OF RHEUMATIC CARDITIS IN CHILDREN

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IT HAS been suggested recently that in any public health program for rheumatic fever, an adherence to strict diagnostic criteria is of primary importance, but that "despite increase in knowledge of rheumatic fever, no specific diagnostic tests have been forthcoming."[1]

Obviously, in any workable program for the care and management of a disease of unknown etiology, a specific, clear-cut method for making a diagnosis is to be ardently desired. It is equally true, however, that when a definite diagnosis has been established, medical care and management will be guided by a clear recognition of all the evasive clinical and subclinical manifestations of the activity of the disease. The burdensome problems confronting physicians and public health officials are concerned with the meaning of rheumatic activity and its duration. When can one be certain that the disease has terminated? What are the diagnostic criteria for the cessation of the active rheumatic process?

It has been the common experience of students in this field that many patients, without obvious clinical or laboratory evidence of rheumatic activity, continue to show progressive cardiac damage. These patients have been suspected of having mild, clinically undetectable, active rheumatic disease. "Subacute carditis, which is insidious and subclinical, occurs more frequently than the acute phase of the disease."[2]

It is also widely held that the recurrence risk in rheumatic disease is significantly higher, the shorter the lapse of time from the cessation of the active rheumatic episode.[3] In addition, it is well known that patients having had active rheumatic carditis, have a greater recurrence risk than those without a history of carditis. These observations would seem to point to the necessity for a clear definition of rheumatic recurrence, with special reference to the reactivation defined as carditis. Does a patient have an early recurrence of rheumatic disease after an active episode or are the new clinical manifestations a continuation of the active process? The so-called "quiescent interval" might thus be considered as a form of mild rheumatic activity, presenting none of the classical and accepted criteria for rheumatic activity.

In recent years, many laboratory tests have been proposed to measure rheumatic activity. These have established in the mind of the general practitioner, a confident method of determining when the disease is no longer active. While it is widely known that none of these criteria singly, or in combination, can possibly act as an adequate screening method for rheumatic activity, a great reliance is placed upon them even by those who have seen, repeatedly, many exceptions to the rule. It is true that the student of rheumatic disease does not consider the many laboratory methods as specific tests

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for the diagnosis of the disease, but he is inclined to consider them as pertinent "in evaluating the presence of active rheumatic fever."[1]

It is the purpose of this paper to evaluate the laboratory aids in the diagnosis of active rheumatic carditis, and to describe some of the clinical criteria which have been found helpful in making a diagnosis of smoldering active rheumatic carditis in the absence of the usual positive laboratory evidence.

PATIENTS STUDIED

Two hundred boys and girls, 6 to 14 years of age, were observed at the St. Francis Sanatorium for Cardiac Children, from the beginning of an episode of rheumatic carditis to the end of the active process and for a minimum of six months following this period. All of these cases had a definite diagnosis established on the basis of both clinical and laboratory evidence. Children who showed clinical signs of heart failure were excluded from this study. Some of the children received only small doses of salicylates. This medication was discontinued as soon as the symptoms of arthralgia had subsided. The group received good nursing care, a balanced diet, and moderate amounts of synthetic vitamins. Any child who had an intercurrent infection or illness which might affect the clinical or laboratory course of the carditis, was excluded from this study. Thus the two hundred children were those who were admitted in the early part of an acute rheumatic episode, but who continued to present evidence of protracted carditis without obvious decompensation.

METHOD OF FOLLOW-UP

The work-up in each case consisted of a complete clinical and laboratory examination as well as cardiographic and immunologic studies. Repeated and frequent studies were made. It was soon discovered that many children who presented normal laboratory tests continued to show clinical evidence of carditis. Thus, no child was considered as being eligible for a return to normal activities until both laboratory and clinical evidence of active rheumatic carditis had subsided. When all of the children were considered as being quiescent, an analysis showed that in many cases none of the current laboratory tests used singly, or in combination, were helpful in arriving at a decision as to whether activity was present. Frequent, careful, clinical examinations of the patient thus became an essential part of the follow-up routine.

I. *Clinical and Laboratory Measurements.*—

A. *Leucocytosis:* The value of the leucocyte count as an index of rheumatic infection in children has been discussed for more than two decades.[4] Some observers found it helpful in the classification of the degree of rheumatic activity.[5, 6]

One in every ten of our cases showed no elevation of the white blood count at any time during the entire course of active rheumatic carditis. Nine of every ten showed a leucocytosis during the first two weeks after the onset of the illness, and seven of every ten continued to show such an elevation at the end of the fourth week. No leucocytosis was observed in any of our cases after the seventh week from the beginning of the active episode. All our

TABLE I. LABORATORY TESTS AND RHEUMATIC ACTIVITY

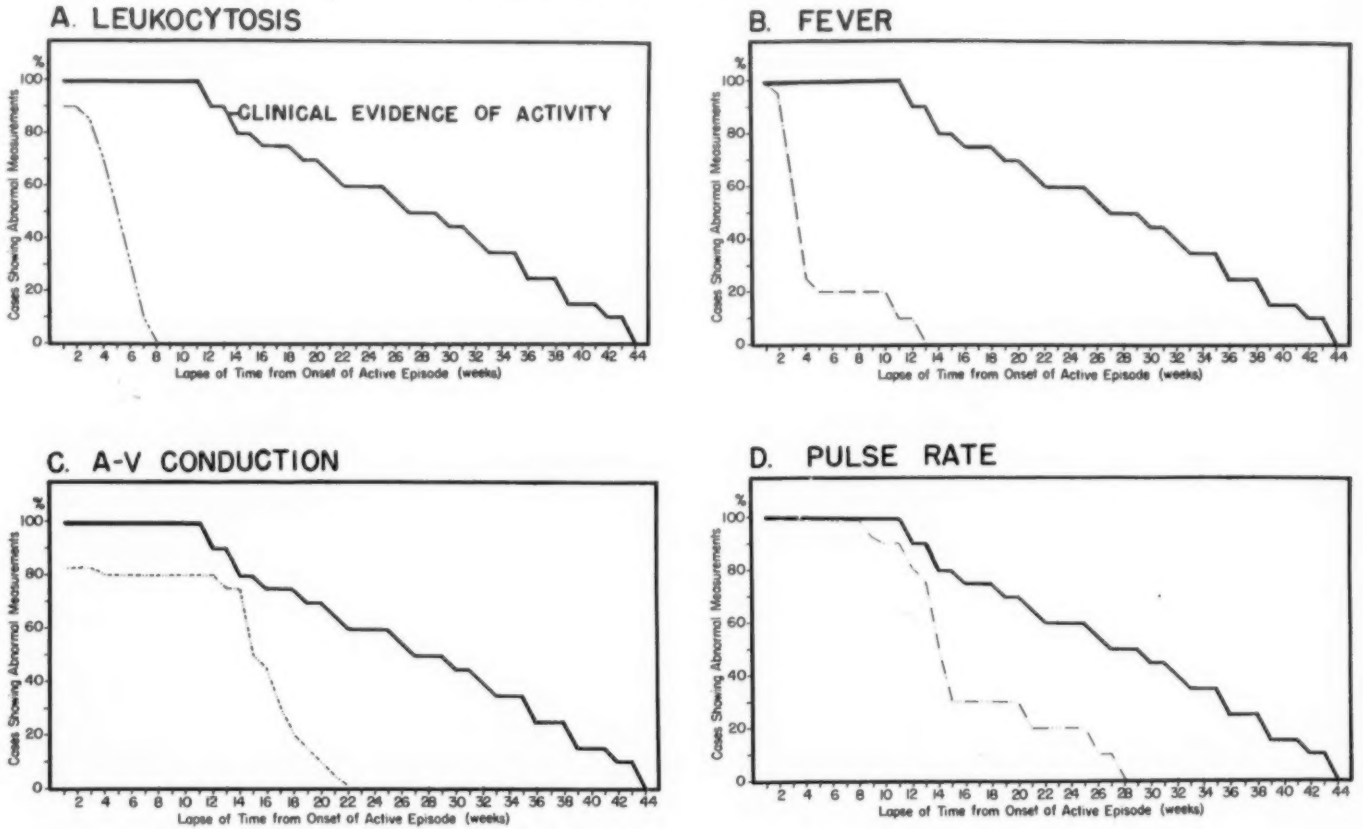
Percentage of cases showing abnormal laboratory measurements in relation to lapse of time from the onset of the active episode

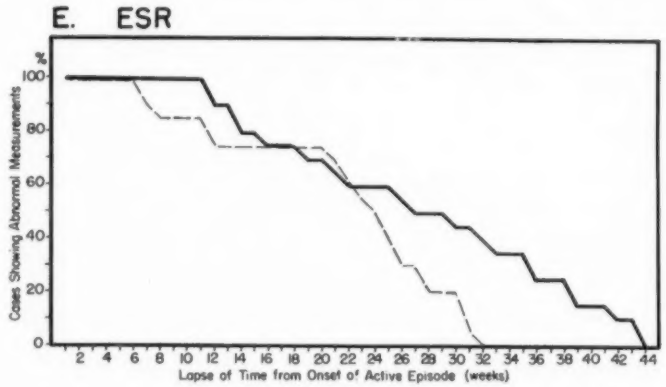
LAPSE OF TIME FROM ONSET OF "ACTIVITY" (WK.)	WHITE BLOOD COUNT A	TEMPERATURE B	P-R INTERVAL C	PULSE RATE D	SED. RATE E	WEIGHT GAIN F	HEMOGLOBIN G	VITAL CAPACITY H	CLINICAL EVIDENCE OF "ACTIVITY"
1	90.0	100.0	82.5	100.0	100.0	100.0	100.0	90.0	100.0
2	90.0	90.0	82.5	100.0	100.0	100.0	100.0	100.0	100.0
3	85.0	60.0	82.5	100.0	100.0	100.0	100.0	100.0	100.0
4	70.0	25.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
5	50.0	20.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
6	30.0	20.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
7	10.0	20.0	80.0	100.0	90.0	90.0	100.0	100.0	100.0
8	0.0	20.0	80.0	100.0	85.0	90.0	100.0	100.0	100.0
9		20.0	80.0	92.5	85.0	85.0	100.0	100.0	100.0
10		20.0	80.0	90.0	85.0	85.0	100.0	100.0	100.0
11		10.0	80.0	90.0	85.0	85.0	100.0	100.0	100.0
12		10.0	80.0	80.0	75.0	85.0	85.0	100.0	90.0
13		0.0	75.0	75.0	75.0	85.0	85.0	100.0	90.0
14			75.0	50.0	75.0	85.0	85.0	100.0	80.0
15			50.0	30.0	75.0	85.0	85.0	100.0	80.0
16			45.0	30.0	75.0	85.0	80.0	75.0	75.0
17			30.0	30.0	75.0	60.0	80.0	75.0	75.0
18			20.0	30.0	75.0	60.0	80.0	75.0	75.0
19			15.0	30.0	75.0	50.0	80.0	75.0	70.0
20			5.0	30.0	75.0	50.0	80.0	70.0	70.0
21			5.0	20.0	70.0	50.0	70.0	70.0	65.0
22			1.0	20.0	60.0	50.0	65.0	70.0	60.0
23				20.0	55.0	50.0	60.0	70.0	60.0
24				20.0	50.0	40.0	50.0	60.0	60.0
25				20.0	40.0	40.0	30.0	60.0	60.0
26				10.0	30.0	40.0	30.0	60.0	55.0
27				10.0	30.0	40.0	30.0	60.0	50.0
28				0.0	20.0	20.0	20.0	60.0	50.0
29					20.0	20.0	20.0	60.0	50.0
30					20.0	20.0	20.0	60.0	45.0
31					5.0	10.0	15.0	60.0	45.0
32					0.0	0.0	0.0	50.0	40.0
33								35.0	35.0
34								20.0	35.0
35								10.0	35.0
36								0.0	25.0
37									25.0
38									25.0
39									15.0
40									15.0
41									15.0
42									10.0
43									10.0
44									0.0

Two cases showed a prolonged A-V Conduction after cessation of rheumatic "activity"

NORMAL VALUES

Temperature: (Rectal) 97.5 to 99.5° F. (36.5 to 37.5° C.)
White blood count: 7,000 to 8,500.
Pulse rate: (Sleeping) 65 to 85 per min.
P-R interval: (See Text, A-V Conduction).
Erythrocyte sedimentation rate: 2 to 12 mm. per hour.
Weight gain: Monthly gain according to age. (See reference.[11])
Hemoglobin: 12.5 to 15.0 Gm.
Vital capacity: (See reference.[2])


A. LEUKOCYTOSIS
CLINICAL EVIDENCE OF ACTIVITY
B. FEVER
C. A-V CONDUCTION
D. PULSE RATE
Cases Showing Abnormal Measurements
%
0
20
40
60
80
100
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Lapse of Time from Onset of Active Episode (weeks)


E. ESR
%
100
80
60
40
20
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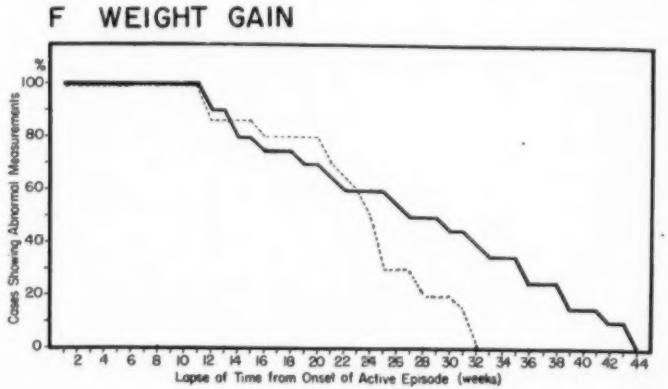
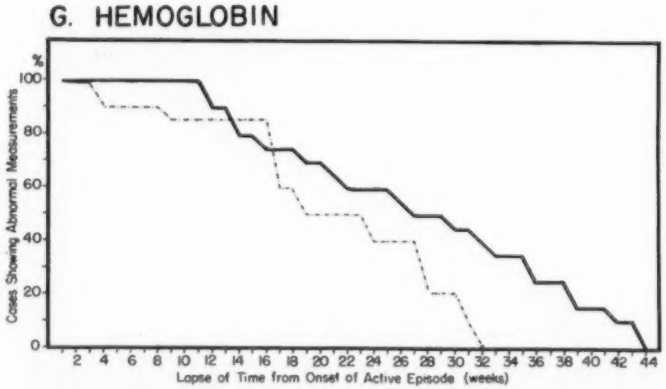
Cases Showing Abnormal Measurements
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Lapse of Time from Onset of Active Episode (weeks)


F WEIGHT GAIN
%
100
80
60
40
20
0
Cases Showing Abnormal Measurements
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Lapse of Time from Onset of Active Episode (weeks)


G. HEMOGLOBIN
%
100
80
60
40
20
0
Cases Showing Abnormal Measurements
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Lapse of Time from Onset of Active Episode (weeks)

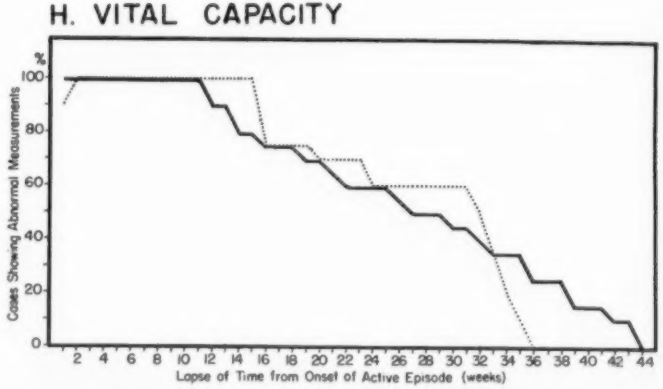

H. VITAL CAPACITY
%
100
80
60
40
20
0
Cases Showing Abnormal Measurements
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Lapse of Time from Onset of Active Episode (weeks)

Fig. 1.—Percentage of cases showing abnormal laboratory measurements in relation to lapse of time from the onset of the active episode.

cases with a leucocytosis at the onset showed a definite decline in the total white blood count with the lapse of time from the onset. It is significant that, while all cases having a leucocytosis had obvious manifestations of clinical rheumatic activity, nine of every ten cases continued to show clinical evidence of active rheumatic disease after the total white blood count had returned to normal. (Table I, column *A*.) (Fig. 1, *A*.)

B. *Fever:* Both in private and hospital practice, a low-grade fever in a rheumatic patient is looked upon as a highly probable manifestation of rheumatic activity. A flat temperature curve is the commonest measurement upon which physicians rely in the assessment of the cessation of active rheumatic disease. Experience with rheumatic children shows that "fever alone is a common erroneous basis for a diagnosis of rheumatic fever."[1]

Fever as a significant manifestation of cessation of rheumatic carditis is not borne out by our observations. All of the cases showed a mild febrile course for a minimum of one week from the onset of activity. The greatest majority of patients, however, remained afebrile after the twelfth week from the onset of the acute process, and the average febrile period for the entire group was six weeks. Only one fifth (20 per cent) of the patients had a low-grade fever after the fifth week, and the longest febrile period was twelve weeks. It is of interest that those patients who showed a temperature level of more than 102° F. (38.9° C.) showed obvious signs of acute exudation, such as pericarditis, pleuritis, or definite joint manifestations, while those who had a fluctuating temperature at a level of less than 101° F. (38.4° C.) showed no such signs. While it is true that all the patients during the febrile period, showed obvious signs of active rheumatic disease, the greatest majority (90 per cent) continued to demonstrate rheumatic activity after the temperature was completely normal. (Table I, column *B*.) (Fig. 1, *B*.)

C. *Auriculoventricular Conduction:** Disturbance in auriculoventricular conduction time has been considered as reliable evidence of the presence of active rheumatic disease in the auricular muscle. It has been suggested that this finding may be seen in the greatest majority of active rheumatic cases if frequent tracings are taken.[7]

The finding of a prolonged auriculoventricular conduction time in a rheumatic patient has come to be regarded as evidence of rheumatic carditis even in the absence of other laboratory or clinical evidence of rheumatic disease, and many a patient has been thus stigmatized, as long as his P-R interval has remained prolonged. On the other hand, a return of the P-R interval to normal is looked upon with confidence as a sign of cessation of rheumatic activity.

It is well known that a prolonged auriculoventricular conduction time may be of supracardiac origin.[8] In addition, long follow-up studies of patients with rheumatic disease show that some develop a prolonged A-V conduction as a permanent feature on their electrocardiographic tracing. In our experi-

*Upper Limit of Normal P-R Interval by Age and Cardiac Rate

Age	70	71 to 90	91 to 110	111 to 130	131 and above
6 to 13	0.18	0.17	0.16	0.15	0.14
14 to 17	0.19	0.18	0.17	0.16	0.15

ence, a prolonged P-R interval in a rheumatic patient, without other laboratory or clinical signs of rheumatic disease, cannot safely be regarded as a manifestation of active rheumatic disease and the return of the conduction time to normal does not always mean cessation of activity.

Thirty-five (17½ per cent) of the children did not show any prolongation of the A-V conduction time at any time during the entire course of the active rheumatic process. It is probable that some of these might have shown a prolongation of conduction time, had electrocardiograms been taken at more frequent intervals. Ninety-nine per cent of the children who had a prolonged auriculoventricular conduction time at the onset of the carditis showed a normal conduction time later. However, 75 per cent of the cases showed clinical evidence of active rheumatic disease when the auriculoventricular conduction time had returned to normal. It is of some significance that two cases gave the impression of cessation of the active rheumatic disease, although the auriculoventricular conduction time was still prolonged. Both of these cases showed the same conduction time two years after the cessation of activity. (Table I, column *C*.) (Fig. 1, *C*.)

D. *Pulse Rate:** The fourth clinical manifestation of a return to normal following rheumatic activity was found to be the pulse rate. The elevation of the pulse rate was out of proportion to the elevation of the temperature, both in regard to the degree of elevation and to the period during which the pulse rate was found to be rapid. Thus, the children who had temperatures of 101 to 102° F. (38.4 to 38.9° C.) had an average pulse rate of 140. Similarly, other children whose temperatures had become normal, continued to have a pulse rate of 120 to 130.

The first three weeks after the onset of illness, the pulse rate was found to be higher than at any time thereafter. None of the two hundred cases showed a pulse rate of less than 100 before the end of the ninth week from the onset of the acute episode, and none had an elevated pulse rate twenty-seven weeks after the onset. The most marked decline in pulse rate was observed at the beginning of the tenth week following the onset.

It is noteworthy that four of ten children whose pulse rates remained normal, continued to show some evidence of active rheumatic disease. On the other hand, a few cases that were apparently quiescent, showed an occasional sinus tachycardia. (Table I, column *D*.) (Fig. 1, *D*.)

E. *Sedimentation Rate:* It is generally appreciated that an increase in the erythrocyte sedimentation rate is found in most toxic and infectious diseases. In rheumatic disease, an increase in the erythrocyte sedimentation rate has been considered as the most useful finding in evaluating the presence of rheumatic activity,[1] and some observers are inclined to look upon it as of specific diagnostic, as well as prognostic, significance in rheumatic fever.[10-16]

In our group of cases, the sedimentation rate was not as reliable a guide of rheumatic activity as is commonly reported. Many patients had definite

*Most of these pulse rates have been taken during sleep.[9] It is presumed, therefore, that much of the emotional factor is excluded.

active rheumatic disease, with a normal sedimentation rate.* All children showed marked elevation during the first eight weeks from the onset of the illness, the elevation being most marked during the first four weeks. At the end of eight weeks 15 per cent had normal sedimentation rates but many of these continued to show evidence of active rheumatic disease. After the twentieth week, an increasing number of children showed a normal sedimentation rate, and at the end of thirty-two weeks, the sedimentation rate became normal in all the cases, although 40 per cent of the group still showed some clinical evidence of mild rheumatic activity.

Of equal significance is the fact that at the end of the sixteenth week, a number of the children who failed to show clinical evidence of rheumatic activity, had a slightly elevated sedimentation rate. (Table I, column *E.*) (Fig. 1, part *E.*)

F. *Weight Gain:* Consistent gain in weight has been considered as indicative of the onset of the quiescent phase of rheumatic disease.[2] Our findings do not seem to substantiate this observation.

More than one-half of the children in our series were either normal or above normal weight at the beginning of the rheumatic episode. All children showed some loss in weight during the first eight or nine weeks of the active episode. Eighty-five per cent began to gain weight after the ninth week. Four months after the beginning of the illness, all children in this group were gaining weight consistently, but the average percentage of gain was less than would be expected for age, sex, and duration of the period of observation.

At the end of seven and one-half months from the onset, all children had reached a normal weight gain level,[17] although at this time, 40 per cent of them still showed mild rheumatic activity. During these seven and one-half months, a few children with apparently quiescent cases, failed to gain weight from month to month. This was found true mainly in the group of children below 8 years of age; the older age groups added weight in large amounts as soon as quiescence began. (Table I, column *F.*) (Fig. 1, *F.*)

G. *Hemoglobin:* Secondary anemia is usually present during rheumatic activity, the degree of anemia being related to the severity and the duration of the manifestations of the disease. It is considered a characteristic finding during active rheumatic carditis.[18-21]

All our cases showed a moderately severe anemia at the onset of the acute episode. During the first week, the hemoglobin ranged between 7 and 9 Gm. for the entire group. From the end of the first to the end of the fourth week, there was a further depression in the hemoglobin level so that at this time, the range was only 7 to 8 Gm. At the end of the fourth week, two of the children showed a hemoglobin of 5 Gm. It was only twelve weeks after the onset of the illness that thirty (15 per cent) of the children, showed a hemoglobin of 12.5 Gm. or more, and twenty-four weeks after the onset, one-half of them had a normal hemoglobin level. At the end of twenty-eight weeks, one of every five children still showed a low hemoglobin level, and it was only thirty-two weeks after the onset that the hemoglobin of all the children had returned to 12.5 Gm. or more.

*No evidence of heart failure was observed in this group of children.

It may be said, therefore, that in our group of cases, none showed a normal hemoglobin at the beginning of the illness; the lowest hemoglobin level was found in the period from the second to the fifth week of the illness; and all the children showed a normal hemoglobin eight months after the onset of the illness. In a great many instances, the hemoglobin did not return to normal until the activity had subsided. On the other hand, 40 per cent of the cases showed clinical evidence of rheumatic activity after the hemoglobin had returned to normal. (Table I, column *G.*) (Fig. 1, *G.*)

H. *Vital Capacity:** It is generally agreed that a diminishing vital capacity is one of the earliest signs of left ventricular failure.[22] It has been suggested that a low vital capacity in a rheumatic patient, when all other factors which might influence the vital capacity are excluded, is to be considered as a good index of rheumatic activity in the heart muscle.[23, 24] The reduction of the vital capacity in a rheumatic patient is looked upon as a measure of left ventricular failure, even in the absence of the more obvious signs and symptoms of cardiac insufficiency.

The vital capacity in this group of children seems to be the single index most sensitive of the progress of active rheumatic disease. All children showed a vital capacity of 40 per cent or less below normal for age and body surface.†

For the first three months of the rheumatic activity, none of the children showed a rise in vital capacity. Some began to have a slight elevation three months after the onset of activity. The rise was small and the number of cases few. After the first three months, more cases showed a gradual rise in vital capacity, but none reached normal for age and body surface until sixteen weeks following the onset of rheumatic carditis. At this time, one of every four children had a normal vital capacity. The last case which returned to a normal vital capacity reading was eight and one-half months after the onset. On the other hand, even after this lapse of time from the onset, one-fourth of the children still showed mild clinical evidence of rheumatic activity. Thus, while the vital capacity was the last measurement to return to normal, yet it failed to be a specific diagnostic measurement, as many of the children continued to show clinical evidence of active rheumatic disease, while having a normal vital capacity.

A few children had a low vital capacity but failed to show clinical evidence of rheumatic active disease on repeated examination. (Table I, column *H.*) (Fig. 1, *H.*)

Summary: In summary, then, those laboratory measurements upon which considerable reliance is placed in evaluating the progress of active rheumatic disease, did not seem to be adequate for a diagnosis of activity in our group of cases. At the end of nine months from the onset of rheumatic activity, all children in the group showed normal laboratory data, and yet, a large percentage continued to demonstrate clinically, rheumatic carditis.

Some of the clinical measurements remained abnormal for a longer period after the onset than others. None were adequate in screening all cases of

*Children below 8 years of age were excluded from this group since the vital capacity reading is unsatisfactory at this age level.

†Vital capacity measurements were evaluated according to the chart presented by Dr. May G. Wilson.[2]

active rheumatic carditis. Finally, in some cases, an abnormal laboratory test is registered in an otherwise quiescent patient.

II. *Clinical Observations and Criteria.*—

Appearance of Patient: Fatigability, without evidence of cardiac insufficiency, is the symptom which can be adjudged best from careful observation of the patient, rather than from a provocative inquiry into symptoms of fatigue. The child, who under normal circumstances is anxious to participate in all childhood activities during mild active rheumatic disease devises ways and means for substitution of less vigorous and in some instances completely circumscribed activities, provided he is given the chance to do so.

Emotional instability, which is a concomitant of active rheumatic carditis, capricious appetite, restless sleep, and disturbance in the habits of evacuation and urination, form part of the syndrome of mild rheumatic activity. Marked and frequent fluctuations of expressions of elation and depression are obvious manifestations during this phase of the disease.

From time to time, there appears in the literature, the observation on the part of the clinician that the rheumatic patient presents a typical appearance. The pallor of active rheumatic disease during the acute stage is well known. This is often far greater than one would expect from the level of the hemoglobin.

The discrepancy between the degree of pallor and the level of the hemoglobin continues during the entire active rheumatic process, even in the smoldering phase, when all other signs of activity seem to have come to an end. A close parallelism exists between the degrees of pallor and of fatigability. Afternoon and evening pallor is of greater intensity than that noted after a night's rest. Increase in physical exertion or emotional disturbance accentuates the pallor after the initial increase in coloring following exertion.

These three manifestations are a definite part of the general picture which is presented by the patient who is suffering from mild rheumatic activity. As long as the patient presents these manifestations, active rheumatic disease must be suspected.

Auscultatory Evidence: A marked tachycardia with a tumultuous rhythm has long been recognized in acute rheumatic disease as auscultatory evidence of carditis. A clearly defined gallop rhythm with a rapid or slow cardiac rate has also been considered as evidence of an acute carditis. And, in recent years, a rapid evolution of progressive cardiac damage, i.e., cardiac dilatation and hypertrophy, and increase in the extent of the valvulitis with rapidly advancing signs of cardiac insufficiency, has been looked upon as criteria of acute rheumatic carditis.

The absence of a tachycardia, gallop rhythm, and clear evidence of rapidly progressive cardiac damage in a rheumatic child, is thus considered as confident auscultatory evidence that carditis is at an end.

Frequent and careful observation of large groups of children from the onset to the end of an attack of acute carditis gave the impression that the criteria as described are inadequate in making a diagnosis of a mild smoldering carditis. One of every three cases of carditis failed to show this evidence.

Continuous and detailed follow-up studies of this group showed other auscultatory signs, not clearly defined but apparently significant of an active process in the heart muscle.

The cardiac rates in this group of children were rapid or slow, but always markedly labile. Stimuli, which in quiescent hearts did not disturb the cardiac rate, caused, in this group, marked fluctuations. Furthermore, this fluctuation was of long standing. Physical exertion and emotional disturbance produced a sinus tachycardia of the ticktack type, lasting several hours. Continued bed rest might slow the heart rate to the normal average, only to be markedly accelerated when bed rest was terminated. When, however, active carditis had subsided, this disturbance in cardiac rate was of distinctly lesser degree and of markedly shorter duration. In a quiescent carditis, the return to normal of the accelerated heart rate was measured in terms of minutes; in active carditis, it was measured in terms of hours and, not infrequently, in terms of days.

Cardiac sounds and murmurs in mild carditis were ever-changing. The volume and pitch of both first and second heart sounds varied from day to day and often from beat to beat. Murmurs changed in quality, direction, and extent of transmission. The evanescent character of cardiac murmurs in rheumatic hearts is well known. The frequency and multiplicity of changes observed in this group of children were noted only in the actively inflamed hearts. It would seem that the cardiodynamics responsible for cardiac sounds and murmurs are in a state of flux in active carditis, and stabilize when the disease becomes quiescent.

The cardiac rhythm in active carditis simulates that of an embryocardia, irrespective of the rate. The normal ratio of the duration of systole and diastole is definitely disturbed. The usual one-to-two rhythm is lost and approaches more nearly, a one-to-one rhythm. On auscultation, it would seem that the time interval between the first and second heart sounds is equivalent to the interval between the second and first sounds. It is well known that during exercises, the diastolic period is foreshortened to a greater degree than the systolic period, but the sinus tachycardia after exercises or during fever is distinct from the embryocardia type of rhythm noted in carditis. And this type of rhythm is not modified by cardiac rate, as long as carditis continues. Occasionally, a sinus bradycardia with a one-to-one rhythm is observed in active carditis.

As rheumatic activity subsides, the disturbance in rhythm gradually returns to normal. The restoration period to the normal ratio is slow and unstable. In complete physical and emotional rest, the patient, who is definitely approaching quiescence, shows short periods of normal cardiac rhythm. Diastole becomes relatively longer. These periods of normal rhythm are punctuated by intervals of the ticktack variety of rhythm. At this stage, physical exertion or emotional disturbance blots out the periods of normal rhythm and the tumultuous character of the cardiac action is accentuated.

The unstable character of the cardiac rate, the evanescent character of sounds and murmurs, and the disturbance in rhythm were noted in all of our

cases during the initial phase of the acute carditis. In one of every four cases, these auscultatory signs persisted after all laboratory evidence of rheumatic activity had subsided. It is of great significance from the therapeutic standpoint, to note that the group of children showing only auscultatory evidence of carditis, did poorly when permitted to resume normal childhood activities. Some showed symptoms of cardiac insufficiency and a few presented unequivocal evidence of cardiac enlargement after a short period of observation. Many children in this group began to show obvious signs of reactivation. The auscultatory signs of carditis increased and corroborative laboratory evidence became manifest. When, however, all auscultatory signs of carditis had definitely subsided, a return to normal physical activity presented no untoward effects and signs of rheumatic reactivation were not observed.

COMMENT

There is solid evidence that bed rest is the important form of treatment for rheumatic carditis. We are impressed with this concept, notwithstanding the modern tendency to shorten bed rest in cardiac disease. This observation is based upon a large experience with rheumatic children. If management and care of rheumatic carditis is predicated upon this conviction, the importance of diagnostic criteria for rheumatic carditis is obvious. Of even greater importance then, would be the introduction of clear-cut criteria for the cessation of active rheumatic disease. For, once one is certain that the active inflammatory process in the heart muscle has subsided, management can safely be changed from bed rest to normal activities without fear of encouraging further cardiac damage.

In the last few years, much reliance has been placed upon certain laboratory measurements used as criteria for evaluation of the progress of active rheumatic disease. These, we believe, have been placed in improper perspective, relative to their significance as diagnostic criteria. None of the currently used clinical measurements, singly or in combination, can be used as specific diagnostic criteria for active rheumatic carditis.

While abnormal clinical measurements are recorded in all cases of acute carditis at the onset, it is obvious from this group of cases that all of the tests became normal in 25 per cent of the children before the cessation of carditis. It is also apparent that a few cases show no clinical evidence of active carditis while some of the laboratory measurements are still abnormal. These observations would seem to point to the concept that our current laboratory measurements may not be a specific expression of the acute process, but rather a manifestation of specific host-reaction to a disease process. Some patients show a high degree of adaptation to the disease process. In these, the abnormal laboratory measurements return to a normal level readily, although the disease process continues. Other patients show a poor adaptation in this respect. In these, the laboratory measurements continue to be abnormal for a longer period. A few individuals continue to manifest laboratory abnormalities after the disease process has subsided.

Experience with the cases presented in this paper once again brings to the foreground the fact that final decision, as regards the presence or absence of active rheumatic disease, rests upon clinical judgment. This, as in all other medical problems, is a product of continued careful observation and examination of large numbers of children with rheumatic disease over the entire period of rheumatic activity, and for years following the active episode. We are impressed with the observation that clinical assessment of the patient as a whole and careful evaluation of auscultatory findings in an actively inflamed rheumatic heart, are more nearly accurate screening methods for mild rheumatic carditis than those laboratory tests currently adhered to.

SUMMARY

1. Two hundred children with rheumatic carditis were studied under controlled conditions.

2. The observation was made that laboratory measurements, such as temperature, white blood count, pulse rate, auriculoventricular conduction, sedimentation rate, weight, hemoglobin, and vital capacity, are inadequate in finally determining when active carditis has ceased.

3. Clinical judgment and careful observation of the patient and his heart add 25 per cent more cases with a diagnosis of active rheumatic carditis, when all laboratory criteria have failed.

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IMMUNIZATION AGAINST WHOOPING COUGH

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RECENT public health studies[1, 2] on the efficacy of prophylaxis against whooping cough attest to its value, so that by now practically all pediatricians include this immunization, together with diphtheria inoculations and smallpox vaccination, as routine in the care of well children. However, the results, when critically evaluated, are not so good as with prophylaxis against diphtheria. The communicability rate after pertussis immunization remains at 31 to 39 per cent of that for the controls. A re-examination of certain details of immunization has therefore seemed wise. Factors studied were: (1) the age at which immunization was begun; (2) the type of vaccine used; (3) the time interval between injections; (4) the concentration of the vaccine; and (5) the total dosage administered.

(1) *Desirable Age.*—The high mortality rate of whooping cough in the first year of life has led to a number of efforts to secure immunity in very young infants. The inoculation of pregnant mothers with *Hemophilus pertussis* vaccine has been claimed[3, 4] to produce passive immunity in the newborn, but the short life of passive immunity and the lack of clinical evidence of protection seem to have stopped this method. Sauer's[5] experience was discouraging; 8.19 per cent of the infants inoculated under 3 months of age contracted pertussis, as compared with 1.44 to 2.8 per cent for children vaccinated after 7 months of age. Recently, Sako and associates,[6] injecting 3,793 infants under 3 months of age with a total of 40 billion bacteria in the form of alum-precipitated pertussis vaccine, found that 75 per cent of these young infants showed antibody response, as measured by the rapid slide agglutination method.[7]

On the other hand, Miller and associates,[11] using 40 billion *H. pertussis* in aluminum hydroxide as the total dose, "failed to lift the desired 90 per cent of the sera over the 1:320 agglutinin titer level." Their method, being quantitative, is probably more nearly accurate than that of Sako and associates.[6]

It must be re-emphasized that agglutinins, complement fixing antibodies, and opsonins are not protective antibodies, and may or may not measure immunity. Only when a sufficient interval of time has passed to judge clinical immunity (perhaps five years) will it be possible to decide whether true immunity has resulted in these young infants.

To test this question, 20 infants from 3 to 6 months of age received 120 billion *H. pertussis* vaccine in three doses at four-week intervals. Three months later, rapid agglutination tests[7] were performed (Table I). The blood of three infants (15 per cent) was 4 plus; the blood of five infants (25 per cent) was 3 plus; and the others (60 per cent) were negative. Thus, only 40 per cent of the infants immunized between 3 and 6 months of age were positive, whereas when inoculations are postponed until after 6 months of age, from 90 to 95 per cent are positive.

TABLE I.—RAPID AGGLUTINATION TESTS ON INFANTS FROM 3 TO 6 MONTHS OLD RECEIVING 120 BILLION H. PERTUSSIS VACCINE

TOTAL INFANTS	NEGATIVE	3 PLUS	4 PLUS
20	12	5	3
Percentages	60.0	25.0	15.0

(2) *Type of Vaccine.*—The type of vaccine to be used in immunization aroused much discussion in previous years. U.B.A., Pertussis Antigen and Topagen, each had their proponents until Dow[8] showed that all these vaccine fractions lost a considerable portion of their antigenicity. Alum-precipitated vaccines, especially mixtures of *H. pertussis* and diphtheria toxoid, have had a vogue recently, due especially to the insistence of Sauer and associates,[9] that severe reactions could be minimized with "the needle directed distally." Sako and associates,[6] using the small dosages of 8, 12, and 20 billion of the alum-precipitated vaccine in 3,793 infants, observed reactions in 3.3 per cent of the first inoculation, 9 per cent of the second, and 13.6 per cent of the third, with an average of 0.6 per cent abscess formation. They disagree with Sauer and associates stating that the greatest factor in abscess formation was intracutaneous introduction of the alum-precipitated vaccine. Anyone who has seen a number of alum abscesses[10] produced, no matter how the injection is given, will not be so certain. The low pH of alum vaccines, seems to summate the necrotizing power of *H. pertussis*, so that 25 per cent or so produce severe reactions, and 5 per cent produce abscesses.

Semoff,[12] in a comparison of commercial combined or multiple vaccines with fluid toxin, found reactions with alum solutions to be generally more severe and to cause nodules and abscesses, whereas plain fluid toxins gave the best results of all.

This objection to mixed vaccines does not apply to the mixtures of whooping cough vaccine with fluid diphtheria toxoid nor to the mixtures made with aluminum hydroxide (Cutter method). These have been distinctly useful in a technique different from any cited. If the first injection of whooping cough vaccine (40 billion) produced marked pain or fever, the remainder of the 80 billion *H. pertussis* was given in 5 doses of 16 billion each, mixed with 0.5 c.c. fluid diphtheria toxoid. This resulted in a distinct diminution of reactions. Another type of mixed vaccines, the so-called triple immunization, or 3 in 1, against whooping cough, diphtheria, and tetanus in a mixture with aluminum hydroxide[11] resulted, in my experience, in a slightly larger percentage of reactions when used for routine immunization; but it proved very useful for the booster doses given every second year or so. In such cases, the minimal quantities needed for the booster dose resulted in only mild reactions. Thus, if due weight be given to reactions, only the plain *H. pertussis* vaccines of the Sauer (human), Kendrick (sheep), Lilly (bovine), and Cutter (human) types should be given. The possibility of sensitization to vaccines harvested on other than human blood seems to have been nihilified by theoretical demonstration of the improbability of such a phenomenon[13] as well as by the practical experience of many thousands of inoculations. Reactions will occur with any of these vaccines,

but usually they are mild. Occasionally, an infant will respond to the first inoculation with much discomfort and high fever; in these cases, giving the smallest possible quantities in divided doses usually serves to minimize the reactions.

(3) *The Total Dosage.*—The results obtained by Miller and associates,[11] with quantitative agglutination tests, show that even where aluminum hydroxide mixtures are used, a total dosage of 40 billion is frequently insufficient. This must be reiterated, because, unfortunately, many of the commercial mixtures on the market prescribe total dosages of *H. pertussis* clearly insufficient for adequate immunization. The total dosage to be given was originally set by Sauer at 80 billion, but serologic tests[14] showed that a fair percentage of children needed 110 to 140 billion for complete immunization and clinical results of exposures[15] seemed to show that 80 billion were frequently insufficient, while 130 billion usually resulted in complete protection. In a three-year period, the communicability rate of 200 infants the author inoculated with 120 billion was only 9.6 per cent (Table II) as compared with an average of 31 to 39 per cent for those given 80 billion in a previous three-year period.[1]

TABLE II.—COMMUNICABILITY RATE OF 200 INFANTS FROM 6 TO 9 MONTHS OLD RECEIVING 120 BILLION H. PERTUSSIS VACCINE, IN THREE-YEAR STUDY

TOTAL DOSAGE	INTIMATE EXPOSURES	ACQUIRED DISEASE	COMMUNICABILITY RATE
120 billion	52	5	9.6%
80 billion	56	19	33.9%

(4) *The Time Interval Between Inoculations.*—The time interval between inoculations was originally set by Sauer as a week. Clinical results and complement fixation tests[16] suggested that protection would be definitely greater if four-week intervals were employed. This is in line with current immunologic practice in diphtheria and tetanus inoculations.

(5) *The Concentration.*—The concentration or dilution of vaccine employed has similarly experienced many variations in popular favor. The original concentration of 10 billion *H. pertussis* to the cubic centimeter was raised to 20 billion, but the claim that this produced too many reactions resulted in lowering the concentration to 15 billion per cubic centimeter. If 120 billion are to be given, this would necessitate 8 c.c., presumably given as 2 c.c., 2 c.c., and finally 2 c.c. in each arm. No critical analysis of this factor of concentration has appeared in the literature. For this reason, a vaccine with a concentration of 40 billion *H. pertussis* to the cubic centimeter (Cutter) was employed in inoculation of one group of 100 children with 1 c.c. doses at four-week intervals, a total of 120 billion. A second group of 50 children was given 2 to 4 c.c. injections of the 15 billion concentration, and the last group of 50 children was given three 2 c.c. injections of a 20 billion concentration. (Table III.) Each mother was asked to keep a record of evident pain experienced by the infant, to measure the area of inflammatory reaction on the arm, and to record the temperature three times in the twenty-four hours after the inoculation. With a 40 billion concentration of vaccine, 24 per cent experienced pain, 10 per cent showed local induration,

and 21 per cent showed fever above 100° F. With a 15 billion concentration, 30 per cent experienced pain, 12 per cent showed local swelling, and 25 per cent had fever. With a concentration of 20 billion, 25 per cent had pain, 10 per cent showed local swelling, and 25 per cent had fever. These results seem to show no difference in reaction, no matter what the concentration of vaccine employed, at least in a range from 15 billion to 40 billion per cubic centimeter.

TABLE III.—REACTIONS IN THREE GROUPS OF CHILDREN GIVEN VARYING CONCENTRATIONS OF H. PERTUSSIS VACCINE, WITH AN AVERAGE OF THREE INOCULATIONS

	NUMBER	PERCENTAGE PAIN	PERCENTAGE LOCAL INDURATION	PERCENTAGE FEBRILE REACTIONS
Group I.—40 billion concentration; 3 doses of 1 c.c. at four-week intervals	100	24	10	21
Group II.—15 billion concentration; 2 c.c.; then 2 c.c.; and finally 4 c.c. at four-week intervals	50	30	12	25
Group III.—20 billion concentration; 3 doses of 2 c.c. at four-week intervals	50	25	10	25

The differences are statistically insignificant. The question is whether the extra volume introduced by lowering the concentration of vaccine (for a 15 billion concentration, 8 c.c. as compared with 3 c.c. of a 40 billion concentration), does not produce tissue damage which compensates for the concentration.

SUMMARY

An effort to lower the communicability rate of infants immunized with *H. pertussis* in the usual fashion has led to a critical evaluation of certain factors in this routine immunization.

First, the optimum age at which to start immunization for pertussis remains 6 to 9 months. Theoretical analogy with other immunizations and Sauer's discouraging results under 6 months, more than counterbalance the recent report of Sako and associates. In a small group, (20) infants from 3 to 6 months of age, this paper shows a failure of protection as judged by agglutination tests. Until clinical evidences of immunity are forthcoming, as judged by actual protection to exposure, infants should not be inoculated before 6 months of age.

Second, the type of vaccine to be used is reviewed. The use of alum-precipitated vaccines of *H. pertussis* is condemned on the ground of frequent severe reactions, and occasional abscess formation. Sako and associates, using a total dose of only 40 billion, found abscess formation in 0.6 per cent. If the dosage of 80 to 120 billion commonly accepted as necessary for clinical protection were employed, the abscess formation might reach as high as 10 per cent, in the author's experience. The use of combined vaccines, *H. pertussis* with diphtheria toxoid, or with diphtheria toxoid and tetanus toxoid is also condemned on the same ground if the vaccine is alum-precipitated.

Third, the total dosage to be given, originally set at 80 billion, is now recommended to be 120 billion, both on serologic and clinical results cited.

Two hundred infants from 6 to 9 months of age, given 120 billion, showed a communicability rate of only 9.6 per cent as compared with an average of 33.9 per cent for those given 80 billion.

Fourth, the time interval between inoculations, originally set at one week apart, is now recommended to be four weeks apart, both on serologic and clinical experience cited from the literature.

Fifth, the concentration of the vaccine to be employed, originally set at 10 billion to the cubic centimeter, is now recommended to be 20 or 40 billion to the cubic centimeter. A study of three groups of children inoculated with 15, 20, and 40 billion concentrations, with a total dosage of 120 billion, showed statistically insignificant variations in reactions, as judged by pain, local swelling, and fever.

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CRANIOPHARYNGIOMAS IN CHILDREN

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THE CRANIOPHARYNGIOMAS constitute a small but important group of the intracranial neoplasms encountered in childhood. As reported in the literature they comprise about 13 per cent of such tumors. Since they may produce blindness, severe disorders of growth and metabolism, and obstruction to the ventricular system they are important to the pediatrician. To the neurosurgeon they are of extreme importance because they are benign lesions, and hence, theoretically, curable ones. However, because of their environmental relations, the difficulties they present were felt by Cushing[1] to ". . . offer the most baffling problem which confronts the neurosurgeon."

These tumors are described in the literature by a variety of names suprasellar cysts, craniobuccal cysts, Rathke's pouch tumors, adamantinomas, hypophysial duct tumors, interpeduncular cysts, suprasellar epitheliomas, craniopharyngeal duct tumors. Excellent studies of these neoplasms have been made by Duffy,[2] Critchley and Ironside,[3] McLean,[4] Beckmann and Kubie,[5] Frazier and Alpers,[6] and by Love, Shelden, and Kernohan.[7]

The relationship of the so-called craniopharyngiomas to the hypophysial duct was first suggested by Mott and Barrett[8] in 1899, and later established by Erdheim[9] in 1904. Erdheim pointed out that in the embryonic development of the hypophysis from a union of infundibular and buccal pouch components the epithelium comprising the original forward wall of Rathke's pouch comes eventually to form the anterosuperior covering of the anterior lobe of the hypophysis. (Fig. 1.) Squamous cell rests occupying this location have been observed repeatedly in autopsy studies in the absence of neoplasm. Proliferation of these squamous epithelial cells results in the epithelial masses with cyst formation that are known as suprasellar cysts, hypophysial duct tumors, adamantinomas, and craniopharyngiomas. Cushing coined the term "craniopharyngioma" because he felt it was accurately descriptive of the tumor's unique origin. Bremer[10] recently pointed out that from the embryologic point of view this widely accepted term is not accurate, since Rathke's pouch is a diverticulum of the buccal cavity and not of the embryonic pharynx (Fig. 2). The mucosa of the stomodeum is of ectodermal origin and not entodermal as is that of the pharynx. Thus, the hypophysial duct tumors owe their masses of squamous cells to the ectodermal lining of the buccal cavity or stomodeum. The term craniostomodeal cyst is a more nearly accurate designation of these tumors. It seems hardly worth while to suggest the substitution of a new name when craniopharyngioma is well established and clearly understood, even though actually inaccurate.

Sixteen children with craniopharyngiomas have been treated by the surgical services of The Children's Hospital and the Peter Bent Brigham Hos-

From the Department of Surgery of Harvard Medical School and The Surgical Services of The Children's Hospital and Peter Bent Brigham Hospital.

pital during the thirteen-year period of 1932 to 1945 inclusive. This report, from experience with these 16 children, is concerned with the problems encountered and the clinical aspects of craniopharyngiomas in early life. Two case reports will be followed by a general discussion of the problem.

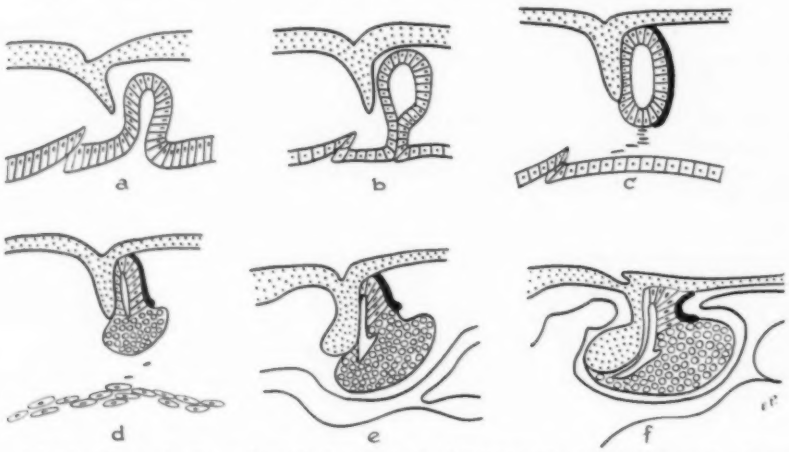

Fig. 1.—Stages in the embryonic development of the hypophysis. Note how the forward wall of Rathke's pouch (heavy black line) comes to form the anterosuperior covering of the hypophysis.

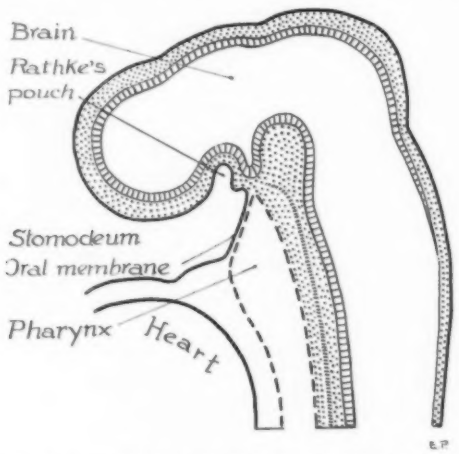

Fig. 2.—Diagram of 2.2 mm. embryo to illustrate the relationship of Rathke's pouch to the stomodeum.

CASE REPORTS

CASE 1.—(A rather typical case of craniopharyngioma in a female child.)

First Admission: N. T. (C. H. #254725). A 6-10/12-year-old girl was admitted to The Children's Hospital on Aug. 20, 1941, because of headaches and vomiting of six months' duration. Past history and family history were irrelevant. Growth and development were normal. The child had been well until six months before admission when she developed mild frontal headaches, occasionally associated with vomiting. She had no visual disturbance,

diabetes insipidus, anorexia, weight loss, ataxia, or paralysis. Headaches and vomiting spells became worse and medical attention was finally sought. Roentgenograms of the skull taken in another hospital revealed separated sutures and calcification above the sella turcica. The child was referred to The Children's Hospital with a diagnosis of craniopharyngioma.

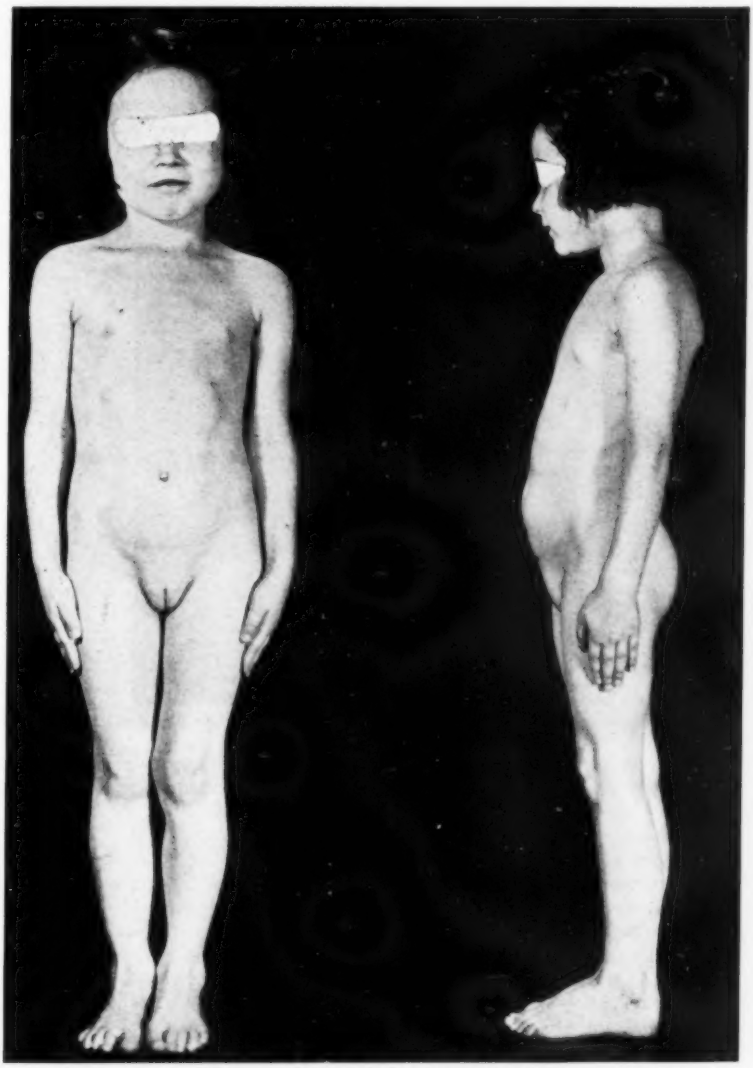

Fig. 3.—Case 1 (N. T.) at time of initial hospitalization, Aug. 20, 1941.

Physical examination on admission revealed an alert, cooperative little girl in a good nutritional state (Fig. 3). Heart, lungs, and abdomen were normal. On neurological examination the positive findings included a positive Macewen's sign, bilateral papilledema of 2 diopters, and hyperactive but equal reflexes. Visual fields were normal. The remainder of the examination showed no abnormalities.

Routine laboratory studies of blood and urine were not remarkable. Blood Hinton test was negative, as was a tuberculin test. Roentgenograms of the skull showed an irregular area of calcification measuring about 1.3 by 0.9 cm. in size, extending upward from the sellar fossa (Fig. 4). The cranial sutures were separated. A diagnosis of craniopharyngioma was made and on the sixth hospital day craniotomy was done, utilizing a coronal scalp incision and a right frontal bone flap. A cyst was exposed behind the chiasm and on aspiration 15 c.c. of dark yellow, oily fluid were obtained. Because of the extent and location of the cyst, no attempt was made to remove it at this time. Twelve days later the bone flap was re-elevated and, employing a transventricular approach, a large portion of the cyst wall was removed from the third ventricle. Pathologic examination of the specimen showed it to be craniopharyngioma.

Fig. 4.—Roentgenogram of skull in Case 1. Note separated sutures and suprasellar calcification.

The child made an uneventful convalescence except for the development of diabetes insipidus of moderate severity. Her pressure symptoms were relieved entirely and she was discharged home on Sept. 30, 1941.

Second Admission: The patient was readmitted to The Children's Hospital on Feb. 23, 1942, because of recurrent headaches. In the five months at home there was progressive loss of appetite and she lost nine pounds. (Fig. 5.) The diabetes insipidus had persisted. She became increasingly weak and tired easily. In the two weeks prior to admission frontal headaches had returned without associated vomiting or visual disturbances.

Physical examination showed a bright, emaciated child with a well-healed coronal scar. Optic discs were quite normal in appearance with neither atrophy nor papilledema. Neurological examination was otherwise unchanged and visual fields remained full. Roentgenograms showed no evidence of intracranial hypertension but there was an increased amount of suprasellar calcification.

Basal metabolic rate was +8 per cent by weight and −13 per cent by height. Fasting blood sugar, 93 mg. per cent; blood chlorides, 114 milliequivalents per liter; sodium, 144 milliequivalents per liter; nonprotein nitrogen, 32 mg. per cent; serum protein, 7.2 Gm. per cent; glucose tolerance test showed a rather flat curve; and urine concentrated to a specific gravity of only 1.010.

Ventriculograms on March 5, 1942, showed considerable dilatation of each lateral ventricle with a large filling defect in the anterior part of the third ventricle. Craniotomy

was then immediately carried out and by transventricular exposure a large recurrence of the cyst was removed from the third ventricle.

The patient had an extremely stormy postoperative course characterized by stupor, swinging fever, and inability to take fluids orally, necessitating gavage feedings. She then embarked on a steady downhill trend illustrating the characteristics of pituitary cachexia

Fig. 5.—Case 1 (N. T.) at time of second hospital admission six months later. Early cachexia.

complicated by severe disturbance of temperature regulation. She developed marked dehydration despite adequate fluid administration (Fig. 6) and was restored to transitory electrolyte equilibrium with the aid of adrenal gland extract therapy. Temporary improvement

in state of consciousness, appetite, and a gain of ten pounds despite discontinuance of substitution therapy occurred during the next two months. However, three months after the last operation she developed ventricular obstruction and again became comatose. One last operative attempt to relieve the obstruction was decided upon. Consequently, on June 9, 1942, the right frontal flap was elevated for the fourth time and again a large recurrence of cystic and solid tumor was removed from the third ventricle. Following the operation she developed a severe pneumonia and died fifteen days later.

Fig. 6.—Case 1 (N. T.) after development of severe pituitary cachexia two months later.

Fig. 7.—Case 1 (N. T.). Sagittal view of brain at autopsy with residual craniopharyngioma in situ.

Autopsy revealed severe emaciation with mild hirsutism and a generalized interstitial pneumonia. A partially solid craniopharyngioma had virtually destroyed the hypothalamus and the structure of the ventral thalamus (Fig. 7). No trace could be found of the tuber

cinereum, infundibulum, mammillary bodies, or hypophysial stalk. There was almost complete atrophy of the posterior part of the hypophysis and great diminution in size of the anterior lobe. The tumor was a craniopharyngioma of the simple squamous epithelial type.

CASE 2.—(A case of craniopharyngioma in a boy with several unusual features.)

A. S. (P. B. B. H. Surg. #78254). A 13-year-old boy was admitted to the Peter Bent Brigham Hospital on July 11, 1945, because of progressive loss of vision of eight months' duration. Past history and family history were noncontributory. Four years before admission the patient had the first of a series of "psychic seizures" which were all of a similar character. These episodes had a sudden onset and were characterized by mental confusion with a "rush of ideas" and were usually followed by a "dreamy state" lasting for two to three hours. These fugue-like spells were unaccompanied by any involuntary movements and occurred ten to fifteen times each year. Mild frontal headaches began to appear about two years before admission and for eight months there had been progressive loss of visual acuity. There were no other complaints. The patient had always been "slightly small for his age."

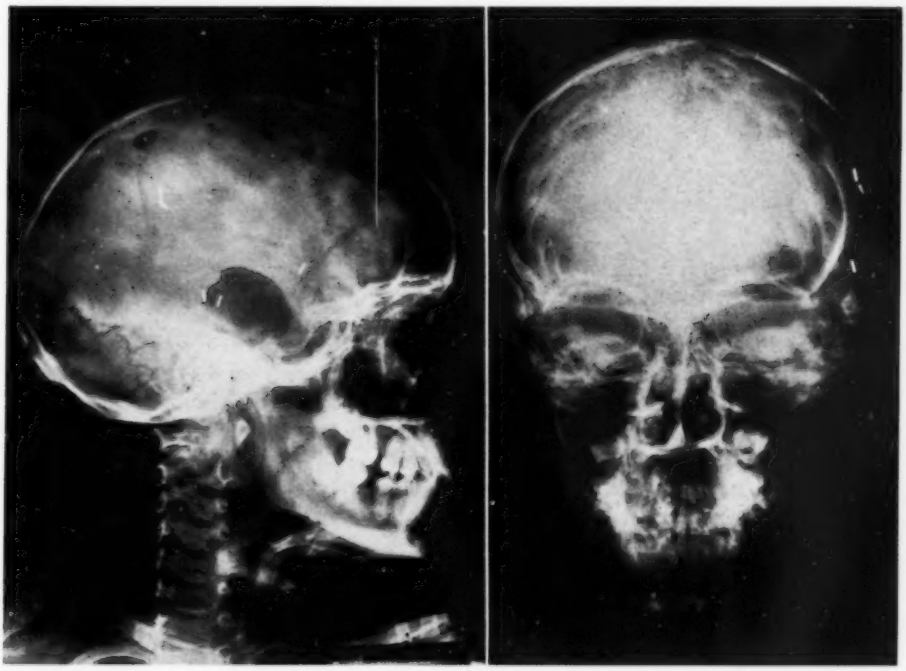

FIG. 8.—Case 2 (A. S.). Roentgenograms of skull with 40 c.c. air injected into residual cystic craniopharyngioma.

Physical examination revealed a rather thin, slightly undersized and underdeveloped 13-year-old male. Heart, lungs, and abdomen were normal. Visual acuity was 20/100 in each eye. Visual fields showed a classical right homonymous hemianopsia with some sparing of central vision. Fundi revealed rather severe optic atrophy on the right and 1 to 2 diopters of papilledema on the left. There was a right facial weakness of the supranuclear type. The remainder of the examination showed nothing abnormal.

Routine laboratory studies were within normal limits. Basal metabolic rate was −30 per cent.

Roentgenograms of the skull revealed increased convolutional markings with slight separation of the cranial sutures. The sella was normal except for atrophy of the posterior clinoids. There was marked thinning of the left temporal bone.

Preoperative diagnoses were: cystic astrocytoma, left temporal lobe; or craniopharyngioma with temporal lobe extension.

A left temporoparietal craniotomy was done on July 19, 1945. A cyst wall was encountered about 2 mm. below the surface of the second left temporal convolution. This was tapped with the removal of about 120 c.c. of clear dark yellow fluid containing cholesterol crystals. The collapsed cyst was then dissected free from the surrounding brain tissue and excised at its base which was found to consist of solid tumor densely adherent to the region of the sella turcica. Pathologic report was craniopharyngioma.

The patient made a smooth postoperative recovery except for a transitory third nerve weakness which had largely returned to normal at the time of discharge.

Three thousand roentgens of irradiation were given in an effort to reduce the tendency to recurrence. Following the roentgen therapy the cyst was tapped through a decompression in the bone flap and 40 c.c. of cyst fluid could be withdrawn and replaced by air, following which roentgenograms were taken to delineate the size and location of the remaining cyst. (Fig. 8.) The patient was discharged home on Aug. 11, 1945. Since his discharge from the hospital he has returned to school and has led an essentially normal life. When last seen, five months after discharge, there was a persistence of hemianopsia but visual acuity was 20/30, and there was no evidence of increased intracranial pressure.

We propose to continue treatment by aspiration of the cyst, resuming roentgen therapy when symptoms reappear.

With these two case reports to illustrate the complex problems which may arise, the more general principles involved may be considered.

PATHOLOGY

Along the anterior aspect of the stalk of otherwise normal pituitaries there are found remnants of the hypophysial duct persisting as islands of squamous epithelium. Neoplastic proliferation of these cells results in the formation of squamous epithelial cysts. These occur most commonly along the pituitary stalk at the level of or above the diaphragma sellae. This accounts for the fact that the anatomic term "suprasellar cyst" has been so frequently used in describing these tumors.

Hypophysial duct tumors are almost invariably cystic, but many of them possess solid portions consisting of masses of squamous epithelium in which calcification frequently occurs. These calcareous masses are likely to lie at the base of the lesion representing the point of attachment of the cyst and its source of blood supply. There is a good deal of variation in the size and gross appearance of these neoplasms. From tiny thin-walled cysts located behind the optic chiasm they may range to huge, complex multiloculated cystic and solid masses which fill and distend the third ventricle, extending upward into the frontal lobes and backward through the interpeduncular fossa against the brain stem.

In the larger cysts the capsule has a smooth, gray-white external appearance, and a fairly tough consistency. The cyst's contents which are composed of desquamated and liquefied squamous epithelial debris, usually consist of an oily brown or golden-yellow fluid resembling motor oil. Floating on the surface and suspended in the fluid one may readily observe numerous glistening

cholesterol crystals. There may be varying amounts of grumous material representing unliquefied epithelial detritus. If the cyst wall is thin, its external surface may be a dark brown or have a bluish hue as a result of the color of the contained fluid.

The lining of most craniobuccal cysts is granular and rough as the result of proliferation of squamous cells with formation of papillary excrescences which frequently undergo keratinization and calcification (Fig. 9).

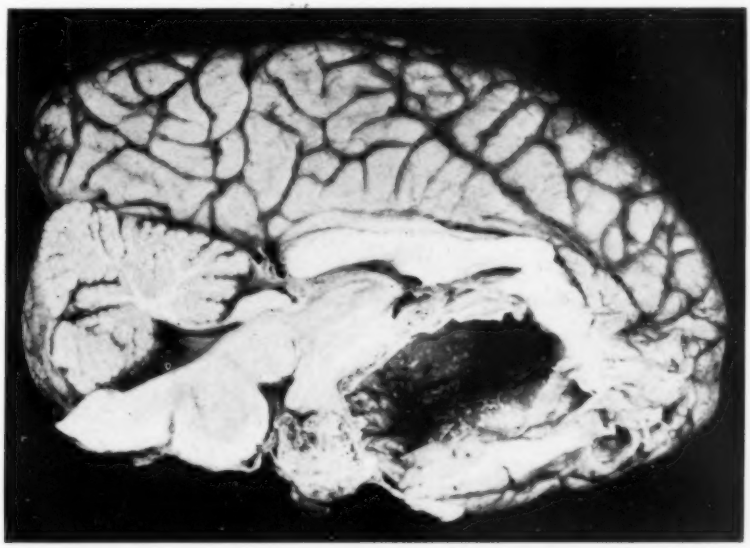

Fig. 9.—Sagittal section of brain of a child with a huge craniopharyngioma. Note smaller solid tumor and superimposed cyst with flecks of calcium in its wall.

There is as much histologic variation in these tumors as there is variety in their gross appearance. This has led to considerable confusion in classification and terminology. Since tumors of the hypophysial duct arise from cell rests of buccal ectoderm they are potentially able to reproduce the various elements of the buccal cavity. Hence it is not surprising that some pathologists have emphasized the resemblance of certain of these tumors to the adamantinomas or ameloblastomas of the jaw. Bailey[11] recognizes three histologic types of tumor having origin in remnants of the hypophysial duct: mucoid epithelial cysts, adamantinomas, and simple squamous epitheliomas.

The mucoid epithelial cysts which he describes are lined by columnar ciliated epithelium and are thought to take origin in Rathke's cleft (hypophysial cleft). Examples of these rare cysts are described by Duffy[2] and by Frazier and Alpers.[12] This type of cyst did not occur in any of our patients.

The adamantinomatous type of craniopharyngioma, according to Bailey,[11] is characterized by the presence of a row of columnar cells arranged in palisade formation next to the connective tissue resembling the adamantoblasts or ameloblasts of tooth-buds. Critchley and Ironside,[3] Peet,[13] Frazier and Alpers,[6] and

others apparently feel that tumors of the hypophysial duct (as opposed to the mucoid epithelial cysts which are presumably tumors of the hypophysial cleft) should be classified as adamantinomas or ameloblastomas. In this group of sixteen cases only one tumor showed histologic structure suggestive of the adamantinoma of the jaw. In the remaining fifteen cases there were tumors which belonged in Bailey's classification of simple squamous epitheliomas.

The essential histologic structure in this common type is that of masses and anastomosing cords of squamous epithelium lying in a stroma of fibrous connective tissue (Fig. 10). The epithelium resembles that of the skin. It is stratified squamous in type, some of the cells having intercellular bridges. The

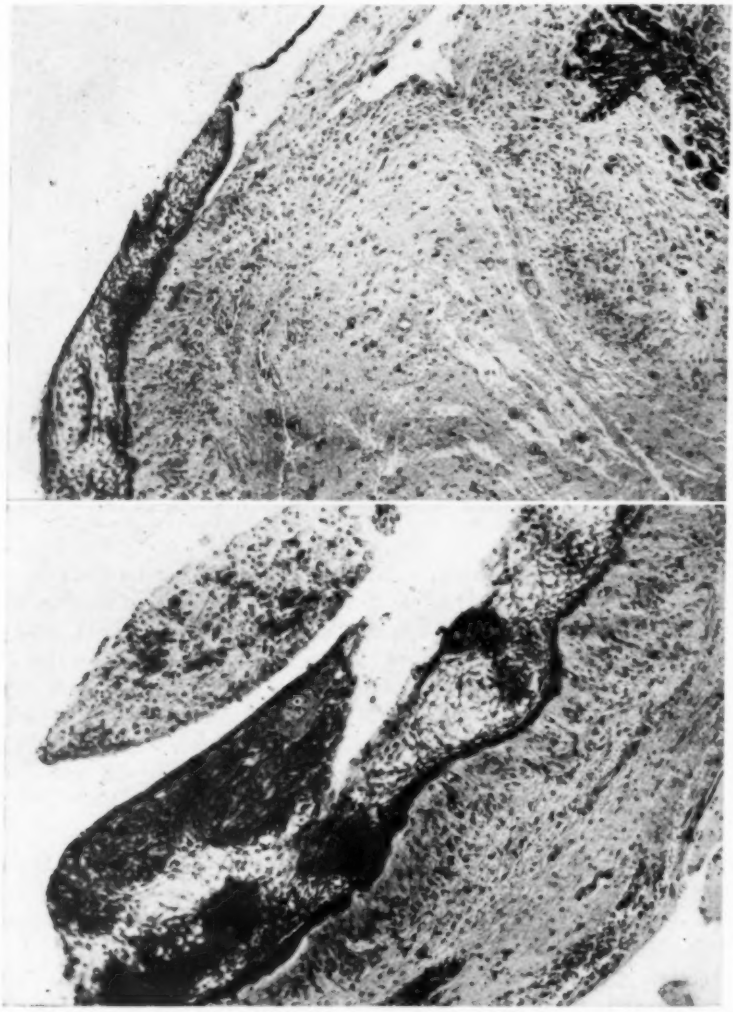

Fig. 10.—Photomicrographs of craniopharyngioma of the simple squamous epithelial type. Note calcification (upper right).

cells nearest the lumen of the cyst undergo keratinization. There is frequently an outer layer of cylindrical cells with central stratification, flattening, and keratinization or cyst formation. The lining of the larger cysts consists of flattened squamous epithelium which is occasionally proliferated so as to form papillae. Calcification is occasionally present in the central area of these papillae. Irregular slits and clefts in the fixed sections are presumed to represent the site of cholesteral crystals. In one of our specimens there was metaplastic bone formation adjacent to the calcified area. The solid masses of the craniopharyngiomas are usually separated from neighboring brain or hypophysial tissue by only a thin layer of gliosis and possess no well-defined capsule. The larger cysts, however, quite frequently have a tough fibrous capsule, which may be continuous with the dura at the base. This capsule is probably derived from the tumor's connective tissue stroma.

No evidence of malignant change was encountered in the specimens removed at operation or in any of the autopsy material. Reports in the literature of carcinomatous types of craniopharyngiomas are difficult to assess because of the frequency with which nasopharyngeal cancer invades the hypophysial region. Peet,[13] however, reported one case in a child of undoubted carcinomatous features developing in an adamantinomatous craniopharyngioma.

Pathologic Physiology.—The common location of craniopharyngiomas in the region of the stalk of the hypophysis makes possible severe physiologic disturbances as a result of the compression of adjacent structures. These disturbances may be grouped under four headings: visual disturbances, intracranial hypertension, hypophysial disorders, and hypothalamic disorders.

The optic chiasm may be compressed from below or above, depending upon the tumor's origin being below or above the diaphragma sellae. Since the most frequent location of the tumor is suprasellar, the chiasm is most commonly pushed downward and forward with production of lower quadrant field defects in the early stages and, later, bitemporal hemianopsia. As the growth of the tumor is frequently asymmetrical, a right or left homonymous hemianopsia may result from optic tract damage. The less common intrasellar or subchiasmal types of the lesion, usually expand anteriorly, rupturing the diaphragma and pressing upward on the chiasm or extending in front of it. Bizarre types of visual field defects, therefore, may be expected from these tumors. However, in some cases there may be no detectable field defects despite the presence of a suprasellar cyst. Primary optic atrophy with early loss of vision may be produced as the result of compression of the optic pathways in the chiasmal region.

Ventricular obstruction may develop when the larger cystic expansions of the tumor extend upward, invaginate the floor of the third ventricle, and either fill the anterior portion of the ventricle or block one of the interventricular foramina. This is extremely common in craniopharyngiomas in children and the acute hydrocephalus which results accounts for the symptoms of intracranial hypertension and subsequent separation of the cranial sutures.

The larger cysts occasionally rupture and spill their highly irritating contents into the ventricular system or subarachnoid space. This results in a severe aseptic ventriculitis and meningitis.

Disturbance of hypophysial function probably occurs in greater or lesser degree in all patients with craniopharyngiomas. In children, probably the most common clinical manifestation of hypophysial deficiency in association with these tumors, is arrested skeletal development. The more severe degrees of anterior lobe deficiency produce the so-called Lorain type of dwarfism with associated sexual infantilism. Pituitary cachexia of the Simmond type is much less common with craniopharyngiomas but was present in two of the children in the group under discussion. Hyperpituitary states such as gigantism, acromegaly, and basophilism are not produced by these tumors. Diabetes insipidus is fairly common in children with craniopharyngiomas and is attributed to damage to the supraoptic nuclei or the supraopticohypophysial tract in the pituitary stalk.

The extension of craniopharyngiomas upward with invagination of the floor of the third ventricle results in compression of the hypothalamic nuclei lying in the floor and walls of the ventricle. More or less destruction of parts of the hypothalamus may result, while varying degrees of stimulation of remaining hypothalamic nuclei may occur simultaneously in the same individual. Bizarre disturbances of hypothalamic function may be produced.

Fulton[14] recognizes five clinical syndromes of the hypothalamus: (1) hypothermia (from damage to the posterior nuclei); (2) hypersomnia (posterior nuclei and mammillary bodies); (3) adiposogenital syndrome of Fröhlich with disturbed fat and carbohydrate metabolism (tuber cinereum); (4) diabetes insipidus (supraoptic nuclei) generally accompanied by hyperthermia; and (5) autonomic epilepsy with manifestations varying with the site of the lesion and presenting a mixture of sympathetic and parasympathetic reactions.

Since the functions of the hypophysis and of the hypothalamus are so closely interrelated and since craniopharyngiomas frequently cause compression of both centers, the clinical syndromes encountered with these tumors can rarely be attributed to individual disturbance of either. More frequently they present features resulting from disturbances of both hypophysis and hypothalamus.

CLINICAL ASPECTS

A. *Incidence.*—In Cushing's[1] series of 2 000 verified intracranial tumors, craniopharyngiomas comprised 4.6 per cent of the total. The age distribution in his group of 92 craniopharyngiomas at the time of symptomatic onset showed 14 for the first decade, 29 for the second, 19 for the third, 13 for the fourth, 9 for the fifth, 6 for the sixth, and 2 patients were over 60 years of age. His youngest patient was 3½ years old.

At The Children's Hospital, 190 intracranial tumors have been verified during the thirteen-year period of 1933 to 1945, inclusive. Twelve of these tumors were craniopharyngiomas, an incidence of 6.3 per cent of the intracranial tumors in children under 15 years of age in a general pediatric clinic. The youngest patient with a craniopharyngioma was 4 years of age, and the oldest was 13 years of age.

The sexes were equally distributed in this group of patients, although some reports in the literature suggest a slight male predominance. There was no indication of any familial incidence in this group of children.

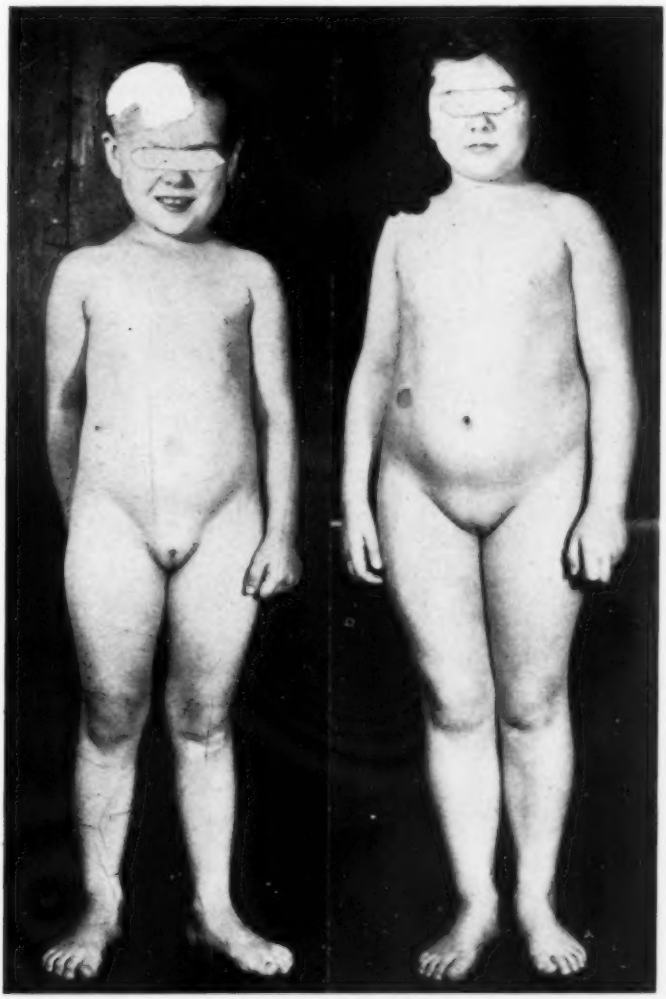

Fig. 11.—Surgical intervention was required by this patient for relief of increased intracranial pressure four times in a period of four years. Note moderate weight increase during this time.

B. *Symptoms.*—The most common initial symptoms of craniopharyngioma in these patients were headache and vomiting, occurring in 15 of the 16 children. This differs markedly from the early symptomatology of this tumor in adults who are more likely to have visual disturbances as a mode of onset, with manifestations of intracranial hypertension as a relatively late occurrence.

Progressive loss of vision occurred in 9 children, 2 of whom were totally blind at the time of hospitalization.

Arrested growth was the third most frequent complaint, being encountered in 5 children. Actual weight loss occurred in 4 children, and progressed to a severe degree of cachexia by the time of admission in one instance (Fig. 5).

Diabetes insipidus had developed in 3 children before hospitalization. This symptom was more commonly encountered as a transitory sequel to operation.

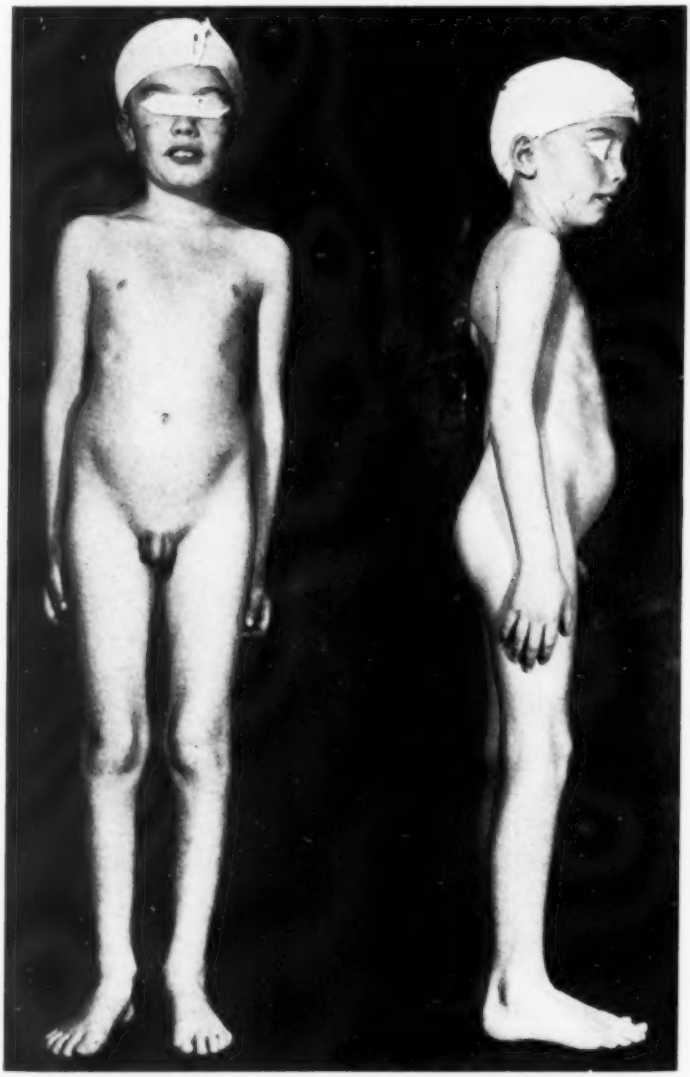

Fig. 12.—Twelve-year-old boy with craniopharyngioma. There had been no apparent growth for four years.

One child had mild convulsive seizures, another had attacks of syncope, and a third had a staggering gait with definite cerebellar ataxia. "Dreamy states" and fugue-like episodes were encountered in the 13-year-old boy (Case 2) whose tumor extended into the left temporal lobe.

Fig. 13.—Photograph of an 8½-year-old girl with craniopharyngioma taken at time of initial hospitalization. Patient had severe cachexia and was in coma on arrival.

Fröhlich's syndrome (dystrophia adiposogenitalis), which has been emphasized in several reports as being the common clinical picture of craniopharyngiomas in children, was not encountered among the patients although one girl showed moderate weight gain during the course of treatment (Fig. 11).

In general, the presenting symptomatology of craniopharyngiomas in this group of children at the time of initial hospitalization was characterized by intracranial hypertension as manifested by headache and vomiting associated with progressive visual loss in more than one-half, arrested skeletal development in less than one-third, and uncommonly, with diabetes insipidus and the overt forms of hypothalamic disorders.

C. *Signs.*—The most consistently positive physical findings in our experience in children with craniopharyngiomas are met in examination of the ocular fundi and the visual fields. Changes in the optic discs on ophthalmoscopic examination were encountered in all of the 16 patients. Bilateral primary optic atrophy was present in 7 children when first studied, while 5 others had bilateral papilledema. Swelling of the nerve heads, bilaterally, combined with abnormal pallor was observed in two individuals. The 2 remaining children showed the fundoscopic changes of the Foster Kennedy syndrome, namely, papilledema in one eye and optic atrophy in the other.

Visual field determinations were carried out on admission in 13 of the 16 children. Fields could not be measured in two instances because of total blindness, and in the case of another child who was brought to the hospital in coma, they were necessarily omitted.

Essentially normal visual fields were found in 5 instances. In 5 others, bitemporal hemianopsia or bitemporal quadrantic defects were present. One child whose cyst had expanded into the left temporal lobe showed a right homonymous hemianopsis. Two other children had lost all vision in the field of one eye and had temporal defects in the other eye field.

Five children were definitely undersize. One 12-year-old boy had shown no growth in the four years preceding admission (Fig. 12). An 8-year-old girl who was admitted in coma showed severe cachexia of the Simmond type (Fig. 13). The other ten children were essentially normal in size, development, and physical appearance.

Macewen's sign (cracked-pot resonance) on percussion of the skull was elicited in 5 children in whom separated sutures were later disclosed by x-ray.

Other abnormalities on neurological examination were strikingly rare in this group of children. Three patients had convergent squint as a result of lateral rectus weakness from sixth nerve palsy. Two others showed a mild hemiparesis with facial weakness of the supranuclear type. Ataxia was present in 2 individuals, leading to a mistaken diagnosis of cerebellar tumor and ultimate suboccipital exploration in one case. In 9 children no neurological changes were elicited other than those disclosed on examination of visual fields and fundi.

Most of these children were mentally alert and in some cases considered to be intellectually precocious.

The systolic blood pressure tended to be normal or slightly subnormal in all of these patients despite the associated intracranial hypertension.

D. *Laboratory Findings.*—Routine laboratory studies of blood and urine at the time of hospitalization were essentially normal in these 16 children,

with the exception of low specific gravity of the urine in the 3 patients with diabetes insipidus. Fasting blood sugar levels were determined in 13 individuals and were within the normal range (90 to 110 mg. per cent) in 10 children, and only slightly low (70 to 90 mg. per cent) in 3 others. Glucose tolerance tests showed a normal curve in 6 patients, and were not carried out in the remainder of the group. The basal metabolic rate was low (below −10 per cent) in 5 children, normal in 2, and not determined in the others prior to operation.

Determinations of 17-ketosteroids and blood iodine were not made in any of the patients before operation was performed. A lowered metabolic rate, associated with a reduced blood iodine level and depressed 17-ketosteroid excretion is indicative of anterior pituitary deficiency in these children. Such studies are probably more valuable in following the course of the disease than in establishing a diagnosis of craniopharyngioma.

E. *Roentgen Findings.*—Roentgenograms of the skull showed definite abnormalities in all the patients with craniopharyngiomas. Calcification above the sella turcica was present in 8 cases, and intrasellar calcification appeared in 2 others. This invaluable finding, which McKenzie and Sosman[15] observed in 71 per cent of craniopharyngiomas in Dr. Cushing's series, is almost pathognomonic of the tumor in children. The visible calcification is most often present in the solid, basal portion of the tumor, appearing in the roentgenogram as a collection of delicate, spongy flecks of opacity (Fig. 4). Rarely, there may be large masses of calcium and, still more rarely, part of the cyst wall may be outlined by calcification.

Roentgenologic evidence of increased intracranial pressure as indicated by separated sutures, convolutional atrophy, or erosion of the clinoid processes, was observed in 7 children. The sella turcica was enlarged and distorted in one-half of the cases. Usually, the enlargement of the fossa is of an irregular type with depression of the floor and is associated with erosion of the dorsum sellae or posterior clinoid processes (Fig. 14).

Significant retardation of bone age, as estimated by examining x-rays of the wrists, was encountered in 5 of this group of children when first seen.

F. *Differential Diagnosis.*—With a history of failing vision, headaches and vomiting, and the finding of calcification in or above the sella turcica on roentgen examination, a diagnosis of craniopharyngioma can usually be made unequivocally in children. Although dermoid cysts, chordomas, and teratomas may occur in the vicinity of the sella, they are much less common and are not likely to show the delicate flecks of calcification so characteristic of the craniopharyngioma. In 10 of these patients no diagnostic difficulties were encountered because of this association of findings.

In those instances in which a chiasmal syndrome is encountered in a child with enlargement of the sella but without calcification, the age of the patient is of considerable aid in excluding pituitary adenoma, as adenomas are extraordinarily rare in childhood. In Dr. Cushing's series of 338 pituitary adenomas, there were only 3 patients under the age of 18, the youngest being

10 years of age.[16] At The Children's Hospital we have seen only 2 children with adenomas in the last 15 years.

In the absence of both calcification and enlargement of the sella, a child with evidence of intracranial hypertension and a chiasmal syndrome presents a more difficult problem in diagnosis. Gliomas of the optic nerves and chiasm usually produce rapid loss of vision and the optic foramina are frequently enlarged on roentgen examination. Tumors of the third ventricle, such as teratomas, colloid cysts, hamartomas, and gliomas, must be considered and ventriculography is usually indicated to clarify the issue in such instances. In spite of this aid it may be impossible to make an accurate diagnosis preoperatively.

Ataxia, which may result from extension of craniopharyngiomas into the interpeduncular fossa and through the incisura tentorii, was described by Bailey.[17] This was so marked in one of our patients that a diagnosis of cerebellar tumor was made and suboccipital exploration performed.

Fig. 14.—Roentgenogram of skull of 7½-year-old girl with craniopharyngioma. Note huge, distorted sella.

Aneurysms of the circle of Willis, and meningiomas of the tuberculum sellae are important in the differential diagnosis of craniopharyngiomas in adults, but are quite unlikely to appear in childhood.

Internal hydrocephalus from any cause, with dilatation of the third ventricle, may occasionally simulate craniopharyngioma in producing chiasmal

signs and erosion of the clinoid processes. The hypothalamic disturbances of a functional nature and the residue of certain of the encephalitides must also occasionally be given consideration.

TREATMENT AND RESULTS

The benign histologic nature of craniopharyngiomas would tend to suggest that complete surgical removal should result in cure. Unfortunately, the environmental relationships of the tumor are such that total removal can rarely be accomplished without the loss of the patient's life. Attempts at radical excision have not infrequently resulted in immediate or early postoperative death from disturbance of hypothalamic function. Conservative operative intervention with evacuation of the cyst and partial removal of the wall has often provided relief from symptoms for a period of years, and has undoubtedly preserved vision in many patients who have survived for varying lengths of time.

Details of operative technique need not be given in this communication. In general we have found a coronal scalp incision the most satisfactory. With the scalp reflected anteriorly, a small right frontal bone flap is turned down and the region of the optic chiasm exposed by retracting the right frontal lobe either intradurally or extradurally. If the lesion cannot be exposed in this way, a transventricular approach can be made by traversing the right frontal pole. It may then be possible to reach the cyst through the right foramen of Monro, evacuate its contents, and remove a portion of the wall. If exploration suggests that a more extensive removal might be advantageously accomplished by a more complete exposure, a left frontal bone flap may be added, the longitudinal sinus and falx divided, and the tumor exposed through incision of the corpus callosum into the third ventricle. The use of this radical approach has seldom been indicated in this series of cases, but on three occasions has proved to be very satisfactory.

The management of those rare instances in which a large cystic craniopharyngioma ruptures into the ventricular system or subarachnoid space entails institution of drainage of ventricular and spinal fluid as an emergency measure. These episodes are characterized by an abrupt change in symptoms with rapid development of signs of meningeal irritation and usually coma. Repeated taps and continuous spinal drainage are necessary in order to remove the extremely irritating cyst contents from the cerebrospinal fluid pathways.

The availability of whole adrenal gland extracts has simplified, somewhat, the care of these patients during the most critical period. By the use of adrenal cortical extracts, the marked fall in blood pressure and tendency to collapse as the secondary results of pituitary disturbance before, during, and after operation, have been successfully dealt with.

Roentgen therapy of these cystic tumors was suggested by Frazier and associates in 1937, at a time when the results of surgical attack seemed unpromising. He and his associates[18] reported four patients (in three of whom the diagnosis had been verified histologically) who improved to a greater extent following surgery and radiation than would have been expected from

surgical treatment alone. Davidoff[19] is of the opinion that certain of the craniopharyngiomas respond well to radiation therapy, although it is impossible to predict which patients may be so benefited. He has recently had the following rather convincing experience: A patient with a proved craniopharyngioma was treated by operation consisting of evacuation of the cyst and partial removal of the wall, followed by radiation. Complete relief of symptoms was obtained for a period of two years. Recurrence at that time was checked by a second course of radiation.

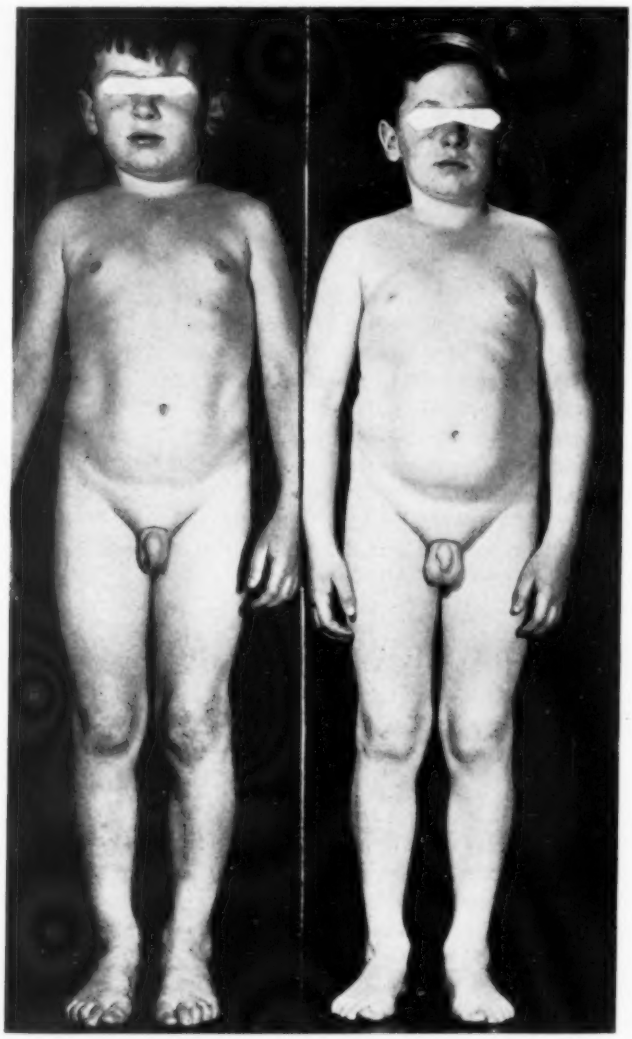

Fig. 15.—Photographs of patient who has survived thirteen years following partial removal of craniopharyngioma. At left, aged twelve years (height 47½ inches, weight 53 pounds); and at right, aged 16 years (height 51 inches, weight 77 pounds).

It has been assumed that the solid portion of the tumor has not been appreciably affected by irradiation but that the cells producing the fluid may have had their secretory character altered. Although many neurosurgeons are of the opinion that radiation of these lesions is quite useless, there would seem to be sufficient evidence to warrant further trial with critical evaluation of results. It should be pointed out that the issue would not be clarified and the patient might suffer loss of visual function if the radiation were carried out without biopsy.

All of the patients were subjected to surgical exposure of the cyst by transfrontal craniotomy with aspiration of contents and removal of as much cyst wall as was readily available in each instance.

Five children are now alive in this group of 16 patients with craniopharyngiomas—a survival rate of 31 per cent. Only 2 of these can be considered "cures" from the standpoint of significant survival. One boy, although retarded in growth, has normal vision and has lived for thirteen years without evidence of recurrence since the partial removal of the cyst (Fig. 15). The other patient, also a boy, is totally blind but has had no return of symptoms for ten years. Less than a year has elapsed since operation on the 3 remaining children.

All the 11 children who died succumbed to the late effects of the tumor or to the direct complications of operative treatment. Repeated operative attacks on the tumor for recurrence of symptoms were carried out in 7 of these patients and 3 children were subjected to as many as four craniotomies in an effort to check the progress of the tumor.

COMMENT

Despite the rather discouraging results obtained by surgical treatment in this group of patients, there is no other logical approach to the problem presented by craniopharyngiomas. A well-planned exposure with aspiration of the cyst and partial removal of its wall can be carried out without mortality in most cases. The diagnosis can thus be verified and symptoms alleviated, albeit only temporarily. There was only one postoperative death following the 16 initial craniotomies in this group of children, and in that instance extensive removal of a solid portion of the tumor had been undertaken. Impending blindness may be forestalled by this relatively simple procedure and in some unusually fortunate cases there may be no return of symptoms for surprisingly long periods of time. Six children treated in this manner showed no evidence of recurrence for periods of one year or longer, and one of these cases has shown no progression of symptoms for thirteen years.

By far the majority of the cases have had recurrence of symptoms in the first three to six months after operation. Some of these children have shown progressive blindness, somnolence, anorexia, cachexia, temperature irregularities, and a few have reached a decerebrate state before exitus. More of them have simply developed return of the symptoms of intracranial hypertension as evidence of refilling of the cyst. Repeated surgical attacks on the tumor have in a few instances prolonged the survival period five or six years, but

the majority of individuals with early recurrence have succumbed in the first eighteen months after the initial operation, despite multiple operative procedures.

In general, it seems logical to conclude that the patients with late recurrence, who have had a relatively long remission following partial removal of the cyst, should be subjected to a repetition of surgical treatment, whereas those with early recurrences and without contraindication such as serious reduction of visual acuity, might best be treated by withholding surgery and instituting roentgen therapy. Our experience with irradiation, in these instances, is too limited to warrant any conclusions, but on the basis of that of Davidoff and others we feel that this plan should be followed until more nearly complete appraisal has been made.

It should be emphasized that most of these children were brought to the hospital for initial treatment only after severe symptoms had developed as the result of cystic tumors of considerable size. By careful study including examination of visual fields and ocular fundi, and careful interpretation of roentgenograms of the skull, it should be possible to recognize craniopharyngiomas in children long before impending blindness, pituitary cachexia, separated cranial sutures, or coma make hospitalization a desperate emergency procedure.

SUMMARY

1. Experience with 16 craniopharyngiomas in children observed at The Children's Hospital and the Peter Bent Brigham Hospital, Boston, during the period of 1933 to 1945, is reported.

2. Two cases are presented in detailed reports.

3. Embryologic, pathologic, physiologic, diagnostic, and therapeutic aspects of craniopharyngiomas in children are discussed.

4. It is suggested that a critical appraisal be made of roentgen therapy as an adjunct to surgery in the management of these tumors.

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The Academy Study of Child Health Services

On May 24, 1946, the Executive Staff of the Study met with the Advisory Committee in order to discuss plans for the analyses and tabulation of data now being collected in the states throughout the country. Dr. Warren R. Sisson, Chairman of the Academy Committee for the Study of Child Health Services attended this meeting.

The discussion was of a preliminary nature and was concerned with plans for the tabulation and analyses of data to determine the availability and receipt of medical care and health services for children in communities or areas of varying geographic, economic, and sociologic character. It was accepted that these plans might be subject to revision as the Study progresses. However, it is appropriate at the present time to publish these discussions for the information of the Academy membership which is fulfilling with notable success its grave responsibility in this enormous undertaking.

In general, the Study of Child Health Services may be divided into three steps: (1) collection of data, (2) tabulation and analyses of the data, (3) preparation of the reports. With the Study programs well underway in 38 states, and all but five states showing some degree of activity, the first step is progressing rapidly. Returns from North Carolina where the pilot study has been conducted are well in hand, with members of the field staff from the Central Office completing the final details in that State. Plans for the tabulation of the results of the pilot study and of subsequent state studies have been under consideration for some time. At this stage it was considered necessary to make some basic decisions as to the handling of the data.

One of the first considerations was to determine the basic classification by which the data are to be tabulated. Inasmuch as the data will be broken down on a county, and where advisable, a city basis, the first problem was to set up the procedure for classification of the counties. Material for the Study is collected by counties because health records are established and maintained on this basis. But counties are political units, and not necessarily comparable geographic or population units. Some are large, some small; some are densely populated, some have few inhabitants; some have high per capita income, some very low. Moreover, listing of facilities available in the more than 3,000 counties of the country would have little meaning. Hence some method of grouping counties with similar traits became necessary.

Three methods of grouping were discussed: (1) metropolitan character of the county, (2) largest urban community in the county, and (3) per capital buying power. Maps of five typical states were prepared on each of these three bases and tables drawn up using already available data to demonstrate to the committee the comparative usefulness of the three methods considered. The Metropolitan character of county method* was selected by the Committee.

A metropolitan county is defined as: (a) one containing a city of 50,000 or more inhabitants, or (b) one adjacent to such county containing a densely populated area of 150 or more persons per square mile in any bordering township. A division of these counties was made by separating those with districts of a million or more people to form a super metropolitan group (Class I).† All other metropolitan counties fall into Class II.

The remaining counties in any state cannot be indiscriminately grouped together as non-metropolitan, because obviously those counties adjacent to large cities have more readily available health facilities and services than others further removed. Therefore, for purposes of classification, all counties geographically adjacent to metropolitan counties are grouped un-

*This classification is based upon one used by the United States Census Bureau, and has been modified and amended by the staff of the Study of Child Health Services with the help and advice of Mr. Elliott H. Pennell, Chief, Statistical Section, States Relation Division, United States Public Health Service.

†Baltimore, Boston, Chicago, Cleveland, Detroit, Los Angeles, New York, Philadelphia, Pittsburgh, St. Louis, San Francisco.

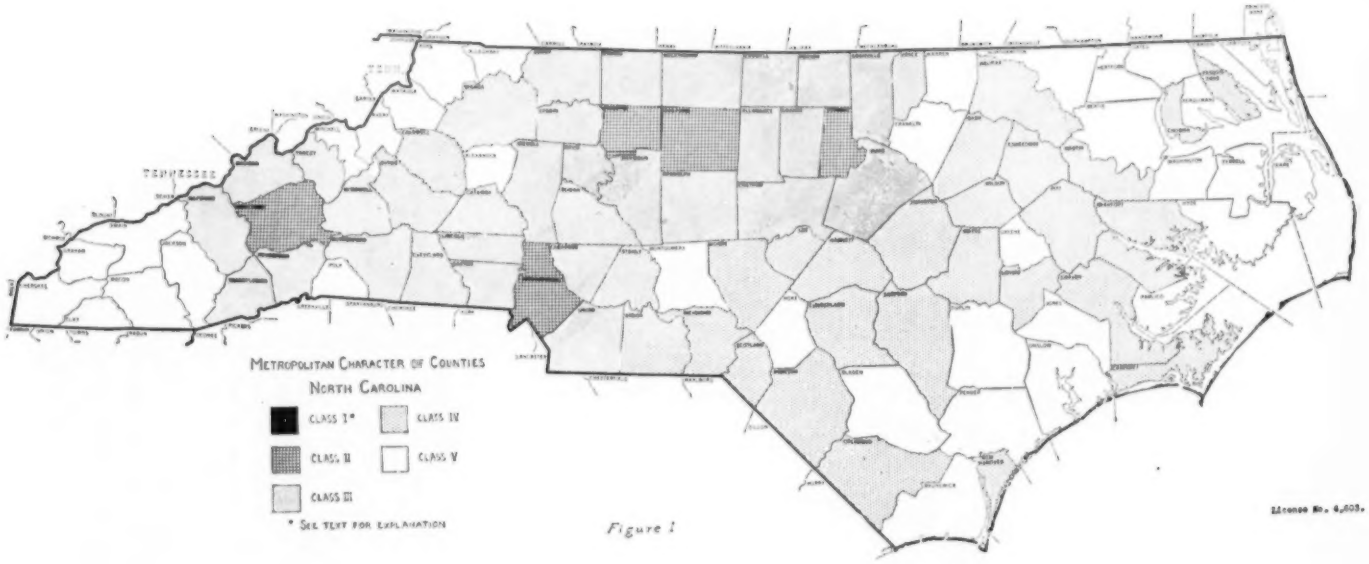

Figure 1

License No. 4,603.

der the title of "First Tier (Class III). The counties on the outer circuit, those at the greatest distance from the metropolitan counties, are called Second Tier, and are subdivided into: (a) those containing incorporated places of 2,500 or more inhabitants (Class IV); and, (b) those containing no incorporated place of 2,500 population (Class V). Table I lists this basic stub, as it is termed, which will be used in analyzing a variety of facilities and services for child health at both the National and State levels.

TABLE I

METROPOLITAN CHARACTER OF COUNTY	NO. OF PHYSICIANS IN PRIVATE PRACTICE	NO. OF PHYSICIANS SEEING CHILDREN	NUMBER OF VISITS PER DAY, BY AGE OF PATIENTS						
			ALL AGES	CHILDREN UNDER 15					PERSONS 15 OR MORE YR.
				ALL	UNDER 1 MO.	1 MO.-1 YR.	1-5 YR.	6-14 YR.	
General Practitioners									
Class I									
II									
III									
IV									
V									
Pediatricians									
Class I									
II									
III									
IV									
V									
Other Specialists									
Class I									
II									
III									
IV									
V									

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To illustrate this classification method, maps of North Carolina (Fig. 1) and Michigan (Fig. 2) are included. It will be noted that North Carolina possesses five counties described as metropolitan (Class II) each containing a city of 50,000 or more inhabitants. North Carolina has no Class I counties. Twenty-six counties are classified as First Tier (Class III), all being adjacent to metropolitan counties. For example, Buncombe County in the western part of the State is metropolitan in character because it contains the city of Asheville (population 51,320); whereas the surrounding or contiguous counties are First Tier by reason of their accessibility to a metropolitan area and its medical facilities. Progressing outward from the centers of population, thirty-three counties described as Second Tier (Class IV) and thirty-six Second Tier Class V) are found scattered throughout the State, the former including within their borders at least one incorporated town or place of 2,500 or more inhabitants, the latter being without any communities of this size. In this way, accessibility to medical facilities, which for the most part are located in larger communities, is graphically demonstrated for every part of the State. In addition, as a further check, it is planned to study road maps showing highways and secondary roads and other transportation routes to determine the accessibility of Class III counties to metropolitan areas.

A map of Michigan (Fig. 2) is presented to illustrate a state containing three Class I counties as well as several Class II counties. Certain other counties in Michigan, though lacking a city of 50,000 or more persons, are considered metropolitan because of other characteristics as already defined. It will be noted that Wayne, Oakland, and Macomb Counties are classified as metropolitan (Class I) by virtue of the fact that they each include part of

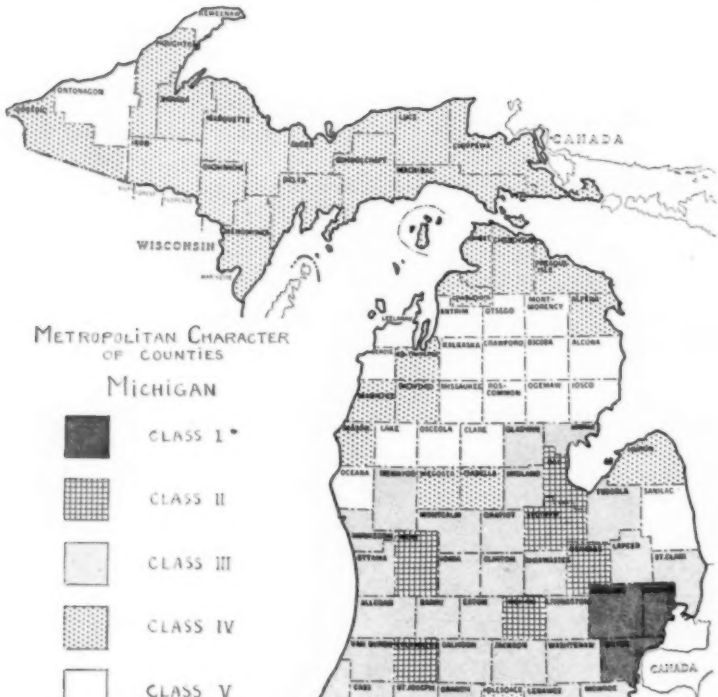

Figure 2.

the metropolitan district of the city of Detroit (population 1,623,452).* Saginaw County is metropolitan in character because its county seat, Saginaw, has a population of 82,794.* Likewise, Bay County is considered metropolitan even though its largest urban community, Bay City, has a population less than 50,000. However, Bay County is adjacent to Saginaw County and contains one or more areas with a density of population of 150 persons per square mile in townships adjacent to Saginaw County.

The committee considered also the forms which the basic tables should assume. Illustrative table forms were presented to demonstrate the methods by which data from the various schedules might be tabulated using the county classification system as the basic stub. Samples of fifteen table forms, similar to Table I, based on material from Schedule III-A were exhibited and discussed in detail.

Certain technical items were also discussed such as ways and means of determining whether returns from physicians and dentists represent a reliable sample for estimating total community professional services for children.

The meeting closed with a brief discussion of the nature and amount of material to be returned to the states. The Acadmy is committed, not only to the task of preparing a report at the National level including tables showing data at the State level, but also to returning to the states tabular material broken down to the level of counties and large metropolitan areas. It was finally decided that the raw data, without attempts at interpretation, should be given back to each state for study and preparation of individual state reports.

*Sixteenth Census of the United States, 1940. Vol. II.

The Social Aspects of Medicine

WAGNER-MURRAY-DINGELL BILL (S. 1050)

Dear Dr. Park:

Senate Bill 1606 is now being given hearings in Washington. This is a modification of the earlier Wagner-Murray-Dingell bill (S. 1050) and is known as the "National Health Act of 1945." This draft differs fundamentally from other versions in that it eliminates (1) the provision dealing with the construction of hospitals and health centers, which is covered in the revised Hill bill (S. 191), and (2) provisions for financing Title II which must be provided in separate legislation. It deals in Title I with: A. Grants to states for public health services. B. Grants to states for maternal and child health services. C. Grants to states for medical care of needy persons; in Title II prepaid personal health service benefits.

Title IA requires no comments as there is quite general agreement in its support.

Title IB. Discussion of the matters contained in this section has been extensive since it follows in general the provisions of the Pepper bill (S. 1318). There is some advantage in having services for children included in the general health plan rather than considered as an independent service.

Title IC. Provides that the states shall determine the "need for medical care." This section sets up a system of medical care for the needy different from that for the rest of the population covered in Title II. It would seem better if the two systems could be combined into a single uniform plan by bringing the needy within the provisions of Title II. Cash benefits for medical care are provided and this is surely undesirable.

Title II provides for a National Insurance System. One's attitude toward this specific piece of proposed legislation is determined in large measure by his concept of government and its function in the social order. Those whose philosophy is based upon security as an ultimate goal will favor a maximum participation of government in community activities. Those who believe in individual responsibility and independence will strive less for security than for freedom and will scrutinize critically any extension of government participation in and control of local affairs. Everyone is agreed upon the desirability of the objective which this title aims to attain—namely better medical care for all the people in the country—but there is wide difference of opinion as to the means by which the goal is to be attained. Furthermore those who are "agitating" for a radical reform in medical practice wish to see results obtained speedily. Those who prefer an evolution rather than a revolution of medical practice, and I count myself among this number, are willing to wait longer for results and believe that the final pattern will be better and rest on a more stable foundation. Rapid change may easily destroy the good features of the present system and lower the quality of medical service.

The great bone of contention in relation to Title II is the insurance principle, whether it shall be voluntary or compulsory. Must everyone be insured or may everyone be given the opportunity to be insured, so far as possible through his own resources but with government assistance when it cannot be met by the individual himself? It is estimated that over 90 per cent of the population would be included under the provision of Title II. One can see how profoundly this would influence medical practice. It would precipitate a system of medical practice on a national scale when experience is lacking as to most of the details involved in its operation. We are not prepared in organization, personnel, or facilities for such a universal application of health insurance. There are many voluntary systems of health insurance which have coverage for certain aspects of medical care but only a few which provide complete coverage. We are certainly quite ignorant as to the costs of the plan as proposed in this legislation but no one has suggested that it will not be very large. I believe that the medical profession should oppose Title II of S. 1606 as it is now written.

The extension of voluntary systems of health insurance with government subsidies for the lower income groups would accomplish everything which this bill serves to accomplish and would have many advantages. It would bring about real changes in medical practice but by a gradual modification of existing methods, not a sudden disruption of a system which, after all, is probably producing better results in national health than have been obtained elsewhere by other methods, some of them in line with the proposals of S. 1606. The gradual development of new features would allow for the simultaneous provision of adequate personnel and facilities to operate the expanded services. The utilization of existing voluntary prepayment groups as the basis for a wider inclusion both of individuals and of coverage would preserve the quality of service rendered and the independence of the persons who are able from their own resources to finance their medical care. It would foster local initiative and minimize governmental control, particularly Federal bureaucracy. It would assure a maximum of professional participation and would, I believe, win the support of the medical profession. It would reduce the cost to the government by a very large sum. Whether at this time the tide can be stemmed is a matter of grave doubt. Unfortunately organized medicine has been slow to appreciate the need for an aggressive attack upon the problems of medical care. It has been too often content with a reiteration of the relatively good medical care in this country as compared with other countries and attributed this to our present system of medical care. It has failed to realize that because a thing is good or even the best in the world that it may not be satisfactory. Fifteen years ago the Committee on the Cost of Medical Care in the majority report recommended certain changes which it believed should be made in the provision of medical care in this country which in the main indicated the lines along which developments have taken place—extension of group practice around hospitals and voluntary prepayment plans. Organized medicine gave lip service to some of the features of this report and openly rejected other features. It has belatedly trailed along in supporting the changes as they have occurred. An opportunity for leadership was lost and one wonders whether it can be regained. Small groups within the profession have from time to time urged a forward looking attitude upon their associates but have met more often with scorn and ridicule than with thoughtful consideration of the ideas put forward. It has been difficult for the minority to present their point of view without provoking an emotional response which made impossible an intelligent discussion and weighing of the evidence.

We are now in a difficult situation. The initiative has been taken out of our hands. Proposals have been made and legislation proposed which, to most physicians, seem unwise and quite likely to result in a lowering of the quality of medical care and involving a tremendous financial tax burden. Is it too late to move forward along lines which give real promise of accomplishing the ends which all desire, better medical care for the American people, or must we accept complete governmental control of medical practice? I do not know but that I am convinced something more must be done, and rapidly, than the cautious pronouncement of projected plans. If energetic action could be taken by organized medicine at once to extend voluntary systems of prepayment for medical care, if real support could be given to the principle of group practice, if efforts could be made to strengthen co-ordinated hospital service and sympathetic tangible support given to public health officials, we might win back popular confidence and lead the way to a better plan than that proposed in S. 1606 Title II. Without such vigorous leadership by the medical profession I see no hope but to gird our loins and work hard under governmental control to safeguard the high traditions of medical care.

RICHARD M. SMITH, M.D.

April 30, 1946

A Criticism of the Article by Professor Lichtenstein Entitled "The System of Medical Care in Children in Sweden" (Journal of Pediatrics, May, 1946)

Dear Dr. Park:

I am enclosing herewith copy for the July issue of the Journal of Pediatrics. I hope that what I have written is the sort of critique you want. If not, I should be very glad to alter it according to your suggestions.

You express in your letter of March 29, disappointment that more discussion regarding systems of medical care is not provoked by a column such as is now running in the Journal. Doctors on the whole think in terms of personal problems and individual patients. One gets the definite feeling that they as well as individual laymen have never really thought through to a real comprehension of what any particular system of medical care would mean for them. Wealthy laymen talk as though a system of compulsory insurance would mean free clinics for them and doctors seem to have a very sketchy idea as to how they would probably lead their lives in the immediate and further future should the Murray-Wagner-Dingell Bill pass. This is an obvious and yet a difficult subject to present but I wonder sometimes if it would not be worth while to attempt.

Thank you for the privilege of putting thoughts on paper.

Very sincerely yours,

Lendon Snedeker, M.D.

Boston, Mass.

In discussing the article of Professor Lichtenstein it would seem helpful to summarize the salient points of the Swedish system as described by him. These are:

1. *State control of Medical Education.*

Education of doctors is completely the charge of the State and is free to all qualified students. This would be at least equivalent to putting all medical education on a State University basis.

2. *State Regulation of all health services* by a National Medical and Health Board.

3. *Voluntary Health Insurance,* available to all the population and now participated in by more than 41.5 per cent of the population over 15 years of age. Insurance schemes in Sweden may be State controlled, partly subsidized by the State or largely independent. Costs of hospitalization are considerably reduced by State subsidy. Insurance includes "sick pay" or the equivalent of disability insurance. The sick fund reimburses the patient. The doctor is left free to charge his own fees and the patient has a free choice of doctor.

4. *State regulation of hospitals and clinics* by the national Medical and Health Board. Local medical facilities are built and operated by the local authorities with the exception of State institutions for the mentally ill.

5. *State control of Pharmacies.*

Pharmacists are government concessionaires and the prices of pharmaceuticals are fixed by the State.

6. *State control of some of the maternal and child health services.*

For Sweden, this system sounds like a satisfactory compromise between State control and individual initiative. Such a system is possible in a country where the general level of education and social conseciousness is high and where the people have faith in the ability and integrity of their government to such a degree that they will submit to considerable regulation. These conditions are not encountered to a similar degree in the United States. Our people are much more impatient of discipline and regulation. Our situation is further complicated by the fact that we are many states with varied population, geography, income, and social standards.

One great objection to the Swedish system is the elimination of the participation by voluntary agencies in education and to a large extent also in hospital and social agency administration. It is our feeling that as long as private philanthropy is able to maintain these voluntary agencies they should be kept as a part of our system. This assures freer

social experimentation. There should, however, be increased opportunities for training in the medical field and government subsidy should be used when and where necessary.

No widespread improvement in health services is possible in this country without some means for more equitably distributing the costs of medical care. The needed funds must come from insurance or taxation. It is our personal feeling that every effort should be made to test out a variety of voluntary medical insurance schemes in this country. These could be independent or state sponsored, but there should ultimately be some means of protecting the interests of the insured person when he moves from one state to another. Doctors should be free to set their own fees, but the system should be sufficiently flexible to permit using other means of remuneration.

Recent experience with compulsory insurance schemes in Italy and with the creaky workings of its old and bureaucratic government, have considerably heightened our apprehensions about the present wisdom of any compulsory national insurance plan. Neither do we think that the present administration of federally controlled health services in this country has shown sufficient flexibility in meeting local problems or in giving the states means of redress against arbitrary administration.

The type of central control and guidance epitomized by the Swedish Medical and Health Board could be emulated to advantage in the United States. Here the first step should be the creation of a Federal Department of Health and a Secretary of Health responsible for the administration of all Federal health agencies.

Our present hospital system needs gradual systematization so as eventually to produce a properly distributed network of institutions adequately equipped and staffed and bound together by ties of mutual respect and cooperation. We have in mind the voluntary plans now operating in Maine and being simulated in other parts of the country. It is obvious that government support and initiative would be necessary in certain parts of the country, but Federal *fiat* cannot take the place of the results produced by local pride and interest.

Dear Dr. Park:

I have studied with much interest the galley proof which you sent me of the System of Medical Care in Sweden. I have understood that medical care was well regulated in Sweden and this article supports such an understanding. Apparently membership in "sick relief funds" is not compulsory but is enjoyed by about one-half the population of the country, and is subsidized by the State.

It also appears that the road to becoming a qualified pediatrician in Sweden is long but made easier by complete state financial support. The author of the article states that for the moment there are "only about 120" qualified pediatricians in Sweden, but on a comparative total population basis this would be equivalent to about 2,500 pediatricians in the United States, where there are only about 1,700 Fellows of the American Academy of Pediatrics. I don't know how many Diplomates there are of the American Board of Pediatrics. [Over 2,600. Editor.]

I am particularly interested in the doctor's final conclusion. With him, I *believe* that "the duty of the state is, however, to organize medical care in such a manner that every person, irrespective of his income, can procure the best preventive and curative medical care." I note he says "can" and not "must."

I *believe* also that it is well established that "the best preventive and curative medical care" is not as well provided under government control as under the control of organized independent doctors.

I further *believe* that, except where health is a matter of community interest as in the case of possible resulting dependence or in the case of contagion, the freedoms for which we have fought should include the freedom to choose one's medical care, or none. There are many persons who, because of religious or other reasons, do not want any care. And is it also not true that except to save a life a surgeon may not operate on a patient against his will?

These three beliefs are compatible: Doctors should continue to organize and run group health cooperatives and associated hospital services; a community government might well give aid such as to underwrite the premium payments of those in the community who are proven too poor to pay them; local government should also assist in providing enough hospital facilities, with help if necessary from the individual State or the National Government; but the citizen should remain free to choose as he will—no medical care, prepaid medical service, or the "pay as you go" system.

Cordially yours,

PHILIP M. STIMSON, M.D.

New York City

My Dear Doctor Park:

I have read and reread Professor Lichtenstein's résumé of the Medical Care Program of Sweden in an effort to understand it and to offer constructive criticism as you requested. After a month of thought on the subject I am unable to do so in a satisfactory manner. As I review the program I am impressed with the thought that it is an attempt to furnish care for everyone with the result that for Sweden it may be very satisfactory. The reaction of one to this program depends entirely upon the viewpoint of the individual. One who is basically socialistic in his viewpoint would perhaps feel that such a program is ideal. To another, equally interested in the welfare of the entire nation but who is basically an individualist, the program would present numerous serious objections. To me the most serious criticism would be that under such a program a large portion of the medical profession of the United States would find it so unattractive that in the future such men would not be attracted to the practice of medicine and the quality of medical care would deteriorate.

I have not submitted specific criticisms of the program which has some excellent features because I would have to go into detail and I do not have sufficient information as to the program. I should be glad to discuss this matter with you some time when the opportunity presents itself.

Very truly yours,

EDGAR E. MARTMER, M.D.

Detroit, Michigan

Dr. Durand in writing me in regard to a personal matter expressed his admiration for the views of Dr. James Wilson published in the February issue of the JOURNAL (28: 231, 1946) and in substance stated that he thought Wilson had put his finger on the crux of the problem and that the development of medicine ought to be in the lines indicated by Wilson, essentially toward the education of more and better educated doctors. I replied asking Dr. Durand if he would be willing to amplify his views in another letter so that I could publish it in the Column and I raised the question if it were possible to embark on a policy of educating more and better doctors unless at the same time there were created some new outlet which created a need. Dr. Durand very kindly acquiesced and the letter from him which follows is the result.

I might add that I, too, liked exceedingly Dr. Wilson's suggestions and think that such a plan as he advocated may be possible, if the Hill-Burton Bill becomes a reality. If the Hill-Burton Bill is passed, the new requirements might furnish the medical schools with a requisite reason and means for increasing their student body and for raising their standards of education.

Dr. Durand's letter is as follows:

E. A. P.

Dear Doctor Park:

I am enclosing a somewhat expanded expression of my views suggested by Dr. Wilson's letter. You can use it if you think it should be published. I think we all feel as you do, that changes are coming and probably without our having much to say about it. I cannot feel that "free" medical care for the children of America is going to bring anything but a rapid deterioration of the quality of such care.

You asked me if Dr. Wilson's suggestion were not equivalent to doing nothing at all. I would certainly rather let the very great progress which has taken place in Pediatrics and the care of children, which I have observed during my 30 years of practice, continue, than to have the Government take the matter out of our hands and do things that I think would greatly harm both patients and doctors.

Perhaps we will not be able to prevent these measures going through, but at least we should make as good a fight as we can for our principles. I think the average doctor cherishes his personal freedom more than any other man in the country and I am sure that 90 per cent of the Academy members are going to feel that the passage of the Pepper bill deprives them of their freedom.

Carrying out the provisions of the bill will mean putting the work in the hands of men as incompetent as those who are now caring for the veterans under the Veterans' Bureau.

I believe the majority of Pediatricians who are now established in practice will refuse to cooperate.

Sincerely yours,
JAY I. DURAND, M.D.

Dr. Wilson's contribution to the Social Aspects of Medicine Department of the February, 1946, JOURNAL OF PEDIATRICS seems to me a very important pronouncement which should be considered by all Academy members and those seeking governmental control of the medical care of children.

It seems to me a self-evident fact that better care for more of our children cannot be provided until we have more well-trained doctors. No amount of tax money spent for "free" care can accomplish this. Rather, it will greatly lower the quality of medical care for two reasons:

First.—There will not be the incentive for men to seek more and more graduate instruction when they are government employees.

Second.—The doctors' offices will be so crowded with children having little or nothing wrong with them that particular attention to the more serious cases will be impossible.

In regard to the governmental care of the sick, pediatricians returning from England tell me that American parents would not wait as patiently nor be satisfied with the brief examinations and explanations of the findings as the English, who seem quite long suffering.

The panel physicians have not had special pediatric training nor is the system conducive to the improvement which comes from personal interest in the individual case and the intensive study of the case and the pertinent literature. In consequence, many children are sent to London for consultation often from considerable distances.

Some of the London pediatricians are quite the equal of any in the world but they are relatively few well-trained men and consequently they can devote little time to each patient.

After coming long distances and, in some instances, waiting several hours, the parents are told very little except that the consultant is sending the information back to the doctor who referred them.

In my experience, I have rarely found such consultations satisfactory to the consultant or very beneficial to the patient.

Comparatively small amounts of tax money spent for educating young doctors, providing them with enough money to live on and even supporting a wife during a two- or three-year period, would raise the quality and increase the quantity of good medical care for children. These men, filling residencies in good hospitals, working under direction in out-patient clinics, would raise the standard generally and provide teachers for those who would follow in their footsteps.

This plan, of course, would not have the political appeal that giving "free" medical care would have and probably will not be seriously considered by politicians, but I do feel that something of this kind must be done if the real progress which we have made during the past forty years is to be accelerated.

JAY I. DURAND, M.D.

The following letter is to correct a misstatement which appeared in the Column in January.

May 10, 1946

Dr. F. F. Tisdall,
Toronto, Ontario

My dear Fred:

It was very kind of you to send me a copy of "Social Aspects of Medicine," which I have read with interest.

By the way, in the letter of Dr. J. Harold Root of 103 North Main Street, Waterbury 14, Conn., the following statement appears: "There is a panel system in England, Australia, New Zealand, Canada, and most of the other government managed plans."

You might like to point out to Dr. Park that this statement of course is incorrect insofar as Canada is concerned—there is no panel in Canada as there is no health insurance in Canada.

With kind regards, I am,

Yours sincerely,

T. C. ROUTLEY,
General Secretary, Canadian Medical Association

News and Notes

The *Annual Meeting of the Academy* will be held at the William Penn Hotel, Pittsburgh, Pa., November 13 to 16, 1946. All hotel reservations will be made through the local convention bureau, and application blanks for hotel rooms will be mailed later to each Fellow.

WANTED—Back volumes of THE JOURNAL OF PEDIATRICS for European medical schools and pediatric clinics.

Requests are being received from England, Holland, Belgium, Sweden, and other European countries for back volumes of THE JOURNAL OF PEDIATRICS either to replace sets lost as the result of enemy action or to complete sets by filling in the volumes which were prevented by the war from entering the countries. Two complete sets have been requested, one of which has already been donated. In addition, for example, there is one request for Vol. 15 (1939) through Vol. 27 (1943), and another for Vol. 19 (1941) through Vol. 27 (1945).

The following single numbers will complete volumes now in the hands of the Editors and make them available for shipping:

Vol. 17 (1941) No. 1, January	Vol. 25 (1944) No. 1, July
Vol. 24 (1944) No. 1, January	Vol. 26 (1945) No. 3, March

With these missing issues plus Vols. 18 (1941), 19 and 20 (1942), 21 and 22 (1942), and 23 (1944) another request can be filled.

Doubtless many more requests will be received and the Editors urge that anyone having a set or the volumes desired who is willing to donate them to the European libraries or clinics will communicate with Dr. Borden Veeder, 3720 Washington Avenue, St. Louis, who will maintain a file of available Journals.

The following promotions of Fellows in Service have been reported to the JOURNAL:

Major Seymour Fisher, Springfield, Ill., to Lieutenant Colonel
Major Daniel J. Pachman, Chicago, Ill., to Lieutenant Colonel

The following Fellows have been released from Service:

Dr. Harry S. Andrews, Louisville, Ky.
Dr. J. Lewis Blanton, Clifton Springs, N. Y.
Dr. Jack Chesney, Knoxville, Tenn.
Dr. Clair L. Douglas, Detroit, Mich.
Dr. A. Alvin Fisher, Canton, Ohio
Dr. Alexander N. Freed, Cleveland, Ohio
Dr. Frederick B. Joy, Seattle, Wash.
Dr. Edmund N. Joyner, III, New York, N. Y.
Dr. Albert P. Knight, Waverly, N. Y.
Dr. Dennis D. Kovan, Detroit, Mich.
Dr. John T. Leslie, Decatur, Ga.
Dr. Matthew M. Lewison, Chicago, Ill.
Dr. Abe Matheson, Chicago, Ill.
Dr. Carl J. Ochs, Cincinnati, Ohio.
Dr. D. William Scotti, New York, N. Y.
Dr. Donald C. Shelby, Beverly Hills, Calif.
Dr. Harry B. Silver, Culver City, Calif.
Dr. Brick P. Storts, Jr., Tucson, Ariz.
Dr. H. Beril Warshall, Brooklyn, N. Y.
Dr. Daniel A. Wilcox, Mt. Kisco, N. Y.

The death of Dr. Joseph C. G. Regan, Brooklyn, N. Y., has been reported to the JOURNAL.